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WO 2004/048309 A1

(54) Title: VITAMIN D RECEPTOR MODULATORS

(57) Abstract: The present invention relates to novel, non-secosteroidal, diaryl compounds with vitamin D receptor (VDR) modulating activity that are less hypercalcemic than 1a,25 dihydroxy vitamin D3. These compounds are useful for treating bone disease and psoriasis.

VITAMIN D RECEPTOR MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

This patent applicaton claims the benefit of priority under Title 35 United States Code, section 119(e), of Provisional Patent Application No. 60/429,041 filed November 22, 2002; the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

Vitamin D_3 Receptor (VDR) is a ligand dependent transcription factor that belongs to the superfamily of nuclear hormone receptors. The VDR protein is 427 amino acids, with a molecular weight of ~50 kDa. The VDR ligand, 1α,25-dihydroxyvitamin D3 (the hormonally active form of Vitamin D) has its action mediated by its interaction with the nuclear receptor known as Vitamin D receptor ("VDR"). The VDR ligand, 1α,25-dihydroxyvitamin D3 ($1\alpha,25(OH)_2D_3$) acts upon a wide variety of tissues and cells both related to and unrelated to calcium and phosphate homeostasis.

The activity 1α,25-dihydroxyvitamin D3 in various systems suggests wide clinical applications. However, use of conventional VDR ligands is hampered by their associated toxicity, namely hypercalcemia (elevated serum calcium). Currently, $1\alpha,25(OH)_2D_3$, marketed as Rocaltrol® pharmaceutical agent (product of Hoffmann-La Roche), is administered to kidney failure patients undergoing chronic kidney dialysis to treat hypocalcemia and the resultant metabolic bone disease. Other therapeutic agents, such as Calcipotriol® (synthetic analog of $1\alpha,25(OH)_2D_3$) show increased separation of binding affinity on VDR from hypercalcemic activity.

Chemical modifications of $1\alpha,25(OH)_2D_3$ have yielded analogs with attenuated calcium mobilization effects (R. Bouillon et. al., Endocrine Rev. 1995, 16, 200-257). One such analog, Dovonex ® pharmaceutical agent (product of Bristol-Meyers Squibb Co.), is currently used in Europe and the United States as a topical treatment for mild to moderate psoriasis (K. Kragballe et. al., Br. J. Dermatol. 1988, 119, 223-230).

Other Vitamin D_3 mimics have been described in the publication, <u>Vitamin D Analogs: Mechanism of Action of Therapeutic Applications</u>, by Nagpal, S.; Lu, J.;

Boehm, M. F., Curr. Med. Chem. 2001, 8, 1661-1679.

Although some degree of separation between the beneficial action and calcium raising (calcemic) effects has been achieved with these VDR ligands, to date the separation has been insufficient to allow for oral administration to treat conditions such as osteoporosis, cancers, leukemias, and severe psoriasis.

One example of a major class of disorder that could benefit from VDR mediated biological efficacy in the absence of hypercalcemia is osteoporosis. Osteoporosis is a systemic disorder characterized by decreased bone mass and microarchitectural deterioration of bone tissue leading to bone fragility and increased susceptibility to fractures of the hip, spine, and wrist (World Health Organization WHO 1994). Osteoporosis affects an estimated 75 million people in the United States, Europe, and Japan.

Within the past few years, several antiresorptive therapies have been introduced. These include bisphosphonates, hormone replacement therapy (HRT), a selective estrogen receptor modulator (SERM), and calcitonins. These treatments reduce bone resorption, bone formation, and increase bone density. However, none of these treatments increase true bone volume nor can they restore lost bone architecture.

Another major disorder that could benefits from VDR mediated biological activity is psoriasis. Psoriasis is one of the most common dermatologic diseases and is a chronic inflammatory skin condition characterized by erythematous, sharply demarcated papules and rounded plaques, covered by silvery micaceous scale.

Synthetic VDR ligands with reduced calcemic potential have been synthesized. For example, a class of bis-phenyl compounds stated to mimic 1α, 25-dihydroxyvitamin D_3 is described in US Patent No. 6,218,430 and the article; "Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1α, 25-Dihydroxyvitamin D_3" by Marcus F. Boehm, et. al., Chemistry & Biology 1999, Vol 6, No. 5, pgs. 265-275.

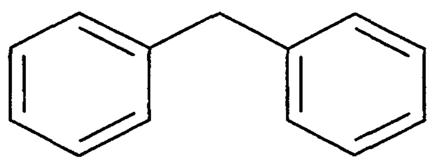
Synthetic VDR ligands having an aryl-thiophene nucleus are described in United States provisional patent application SN 60/384151, filed 29 May 2002.

There remains a need for improved treatments using alternative or improved pharmaceutical agents that mimic 1α, 25-dihydroxyvitamin D_3 to stimulate bone

formation, restore bone quality, and treat other diseases without the attendant disadvantage of hypercalcemia.

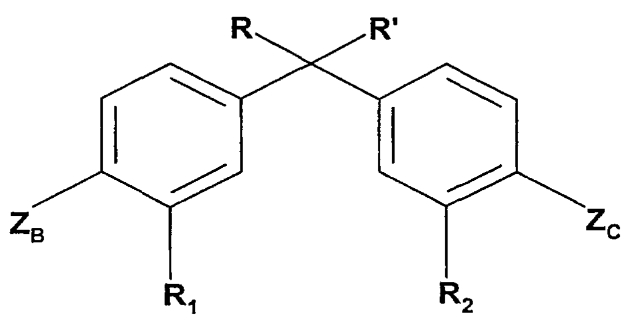
SUMMARY OF THE INVENTION

Novel compounds having a nucleus of formula "(A)" have been found effective as Vitamin D Receptor (VDR) modulators:



(A)

The compounds of the invention with VDR modulating activities are represented by formula (I)



(I)

wherein the variables R, R', R_1, R_2, Z_B, and Z_C are as hereinafter defined. It is a discovery of this invention that compounds described herein display the desirable cell differentiation and antiproliferative effects of $1,25(OH)_2D_3$ with reduced calcium mobilization (calcemic) effects if substituent Z_C possesses a carbon atom linked group that is directly connected (i.e., with no intervening non-carbon atom) to the aryl nucleus.

In another aspect, the present invention is directed towards pharmaceutical compositions containing pharmaceutically effective amounts of compounds of formulae (I) or a pharmaceutically acceptable salt or prodrug thereof, either singly or in combination, together with pharmaceutically acceptable carriers and/or auxiliary agents.

Another aspect of the invention is a pharmaceutical formulation for treatment or prevention of osteoporosis containing pharmaceutically effective amounts of the vitamin D receptor modulator compound of formula (I) alone or together with pharmaceutically

effective amounts of co-agents conventionally used for the treatment of osteoporosis.

Another aspect of the invention is a pharmaceutical formulation for treatment or prevention of psoriasis containing pharmaceutically effective amounts of the vitamin D receptor modulator compound of formula (I) alone or together with pharmaceutically effective amounts of co-agents conventionally used for the treatment of psoriasis.

Another aspect of the invention is a pharmaceutical formulation for treatment or prevention of prostate cancer containing pharmaceutically effective amounts of the vitamin D receptor modulator compound of formula (I) alone or together with pharmaceutically effective amounts of co-agents conventionally used for the treatment of prostate cancer.

Another aspect of the invention is to use the compounds of the invention to treat disease states responsive to Vitamin D receptor ligands.

Another aspect of the invention is the prevention and treatment of acne, actinic keratosis, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone fracture healing, breast cancer, Crohn's disease, colon cancer, Type I diabetes, host-graft rejection, hypercalcemia , Type II diabetes, leukemia, multiple sclerosis, insufficient sebum secretion, osteomalacia, insufficient dermal firmness, insufficient dermal hydration, myelodysplastic syndrome, psoriatic arthritis, renal osteodystrophy, rheumatoid arthritis, scleroderma, seborrheic dermatitis, skin cancer, systemic lupus erythematosis, ulcerative colitis and wrinkles; by administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

The term, "abscess" refers to adverse complications often associated with surgery, trama, or diseases that predispose the host to abscess formation from encapsulated bacteria lymphocytes, macrophages, and etc.

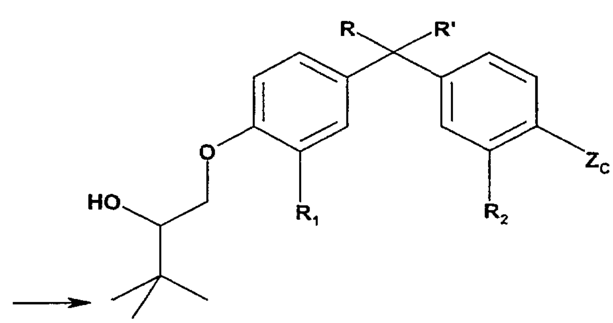
The term, "adhesion" refers to the adverse and abnormal union of surfaces normally separate by the formation of new fibrous tissue resulting from an inflammatory process.

The term, "Mustard" is inclusive of both sulfur mustards and nitrogen mustards, either alone or in any combnation. Examplary of such compounds are the

vesicants; bis(2-chloroethyl) sulfide (Chemical Agent Symbol HD), $Cl(CH_2)_2S(CH_2)_2Cl$ 1,2-bis(2-chloroethylthio)ethane (Chemical Agent Symbol Q), $Cl(CH_2)_2S(CH_2)_2S(CH_2)_2Cl$; bis(2-chloroethylthioethyl) ether, $Cl(CH_2)_2S(CH_2)O(CH_2)_2S(CH_2)_2Cl$ (Chemical Agent Symbol T); tris(2-chloroethyl) amine (Chemical Agent Symbol HN3) $N(CH_2CH_2Cl)_3$; N-methyl-2,2'-dichlorodiethylamine (Chemical Agent Symbol NH2); and 2,2'-dichlorotriethylamine, $CH_3CH_2N(CH_2CH_2Cl)_2$ (Chemical Agent Symbol NH1).

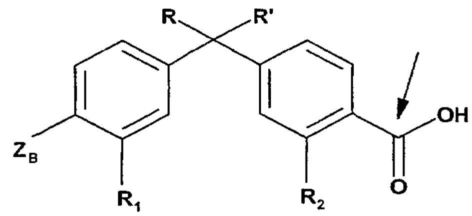
The term "branched C_3-C_5 alkyl" is an alkyl group selected from 1-methylethyl; 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; or 2,2-dimethylpropyl. Preferred branched C_3-C_5 alkyl groups are 2-methylpropyl and 1,1-dimethylethyl, with the 1,1-dimethylethyl group being most preferred.

The term, "branched alkyl terminal group" is used to identify the substituent Z_B of Formula I of the Invention. The defining characteristic of the branched alkyl terminal group is that it is placed on the diphenyl nucleus other than on the phenyl ring bearing the substituent Z_C as shown, for example, in the structural formula (B);



(B)

The term, "carbon atom linked group" is used to identify the chemical substituent Z_C in the Formula I definition of compounds of the invention. Its defining characteristic is a carbon atom as the first atom and point of attachment to the aryl ring to which it is attached. For example in the structural formula (C):



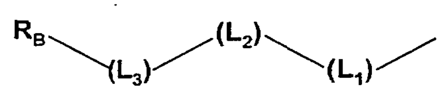
(C)

the arrow identifies the carbon atom linked directly to the aryl nucleus of formula (I). All compounds of the invention contain a carbon atom linked group as the Z_C substituent.

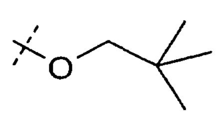
The term "alkenyl" refers to aliphatic groups wherein the point of attachment is a carbon-carbon double bond, for example vinyl, 1-propenyl, and 1-cyclohexenyl. Alkenyl groups may be straight-chain, branched-chain, cyclic, or combinations thereof, and may be optionally substituted. Suitable alkenyl groups have from 2 to about 20 carbon atoms.

The term "C_1-C_5 alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, and cyclic groups and any combinations thereof. Alkyl groups may further be divided into "primary", "secondary", and "tertiary" alkyl groups. In primary alkyl groups, the carbon atom of attachment is substituted with zero (methyl) or one organic radical. In secondary alkyl groups, the carbon atom of attachment is substituted with two organic radicals. In tertiary alkyl groups, the carbon atom of attachment is substituted with three organic radicals. Examples of C_1-C_5 alkyl groups are methyl, ethyl, n-propyl, 1-methylethyl; n-butyl, 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; n-amyl, 1,1-dimethylpropyl; 1,2-dimethylpropyl; and 2,2-dimethylpropyl.

The term, "bond" when used to describe a divalent linking group indicates the absence of a divalent atom, for example in the group



when L_1 is –O-, L_2 is a bond, L_3 is -CH_2-, and R_B is tBu the structural formula is



The term "cycloalkyl" includes organic radicals such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term, "cycloalkenyl" includes organic radicals such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term, "C_1-C_5 fluoroalkyl"is an alkyl group containing fluorine and includes

organic radicals such as $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, and $-CH_2CH_2F$, with $-CF_3$ being preferred.

The abbreviation, "Me" means methyl.

The abbreviation, "Et" means ethyl.

The abbreviation, "iPr" means 1-methylethyl.

The abbreviation, "tBu" means 1,1-dimethylethyl.

The abbreviation, "3Me3OH44DiMe-Pentyl" means 3-methyl-3-hydroxy-4,4-dimethylpentyl.

The abbreviation, "3Me3OH44DiMe-Pentenyl" means 3-methyl-3-hydroxy-4,4-dimethylpentenyl.

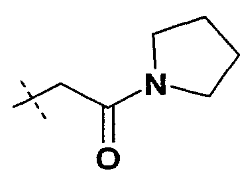
The abbreviation, "3Me3OH44DiMe-Pentynyl" means 3-methyl-3-hydroxy-4,4-dimethylpentyl.

The abbreviation, "3Et3OH44DiMe-Pentyl" means 3-ethyl-3-hydroxy-4,4-dimethylpentyl.

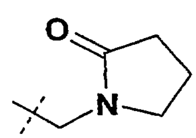
The abbreviation, "3Et3OH44DiMe-Pentenyl" means 3-ethyl-3-hydroxy-4,4-dimethylpentenyl.

The abbreviation, "3Et3OH44DiMe-Pentynyl" means 3-ethyl-3-hydroxy-4,4-dimethylpentynyl.

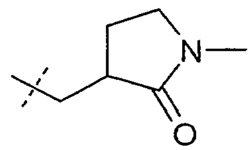
The term, "$-CH_2-C(O)-N$-pyrrolidine" refers to the radical represented by the structural formula:



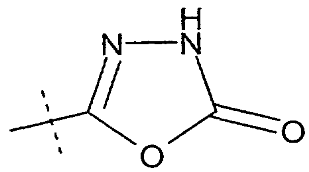
The term, "$-CH_2-N$-pyrrolidin-2-one" refers to the radical represented by the structural formula:



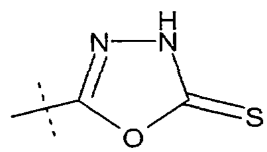
The term, "$-CH_2$-(1-methylpyrrolidin-2-one-3-yl)" refers to the organic radical represented by the structural formula:



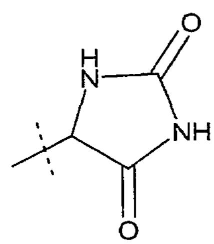
The term, "1,3,4-oxadiazolin-2-one-5-yl" refers to the organic radical represented by the structural formula:



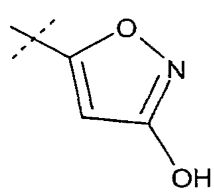
The term, "1,3,4-oxadiazolin-2-thione-5-yl" refers to the organic radical represented by the structural formula:



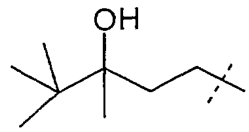
The terml, "imidazolidine-2,4-dione-5-yl" refers to the organic radical represented by the structural formula:



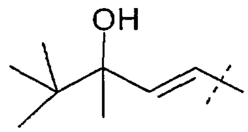
The term, "isoxazol-3-ol-5-yl" refers to the organic radical represented by the structural formula:



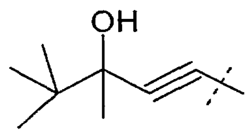
The term, "3-methyl-3-hydroxy-4,4-dimethylpentyl" refers to the radical having the structural formula:



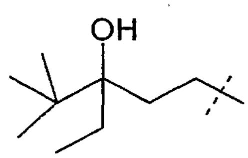
The term, "3-methyl-3-hydroxy-4,4-dimethylpentenyl." refers to the radical having the structural formula (both cis and trans isomers):



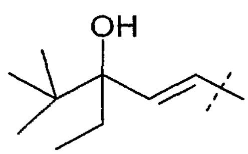
The term, "3-methyl-3-hydroxy-4,4-dimethylpentyl" refers to the radical having the structural formula:



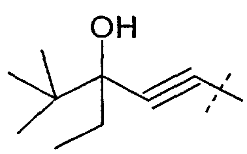
The term, "3-ethyl-3-hydroxy-4,4-dimethylpentynyl" refers to the radical having the structural formula:



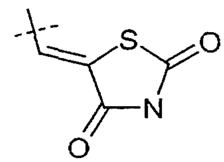
The term, "3-ethyl-3-hydroxy-4,4-dimethylpentenyl" refers to the radical having the structural formula (both cis and trans isomers):



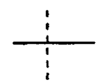
The term, "3-ethyl-3-hydroxy-4,4-dimethylpentynyl" refers to the radical having the structural formula:



The term, "-5-ethylidene-1,3-thiazolidine-2,4-dione, refers to the radical represented by the structural formula:

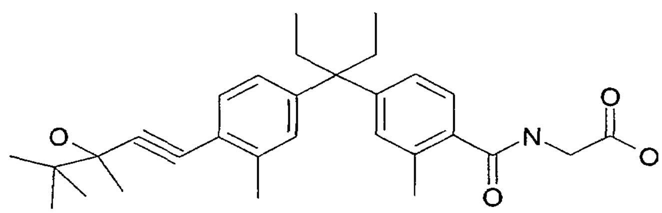


The dotted line symbol crossing a solid line representing a bond

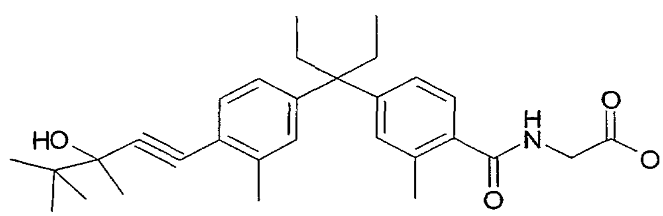


means that the bond so marked is the bond of attachement.

The structural formula representing the compounds of the invention with or without open display of all pendant hydrogen atoms are equivalent, for example:



is the same compound as



The term, "mammal" includes humans.

The term "ester" refers to compounds of the general formula; RO-C(O)R', prepared for example, where a hydroxy group of an acid is replaced with an alkoxide group. For example, a carboxylic ester is one in which the hydroxy group of a carboxylic acid is replaced with an alkoxide. Esters may derive from any acid comprising one or more hydroxy groups: for example, carbonic acid, carbamic acids, phosphonic acids, and sulfonic acids.

The term "halo" refer to fluorine, chlorine, bromine, and iodine.

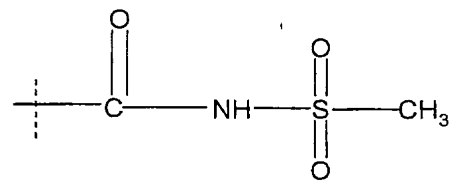
The term, "C_1-C_5 fluoroalkyl"is an alkyl group containing fluorine and includes

organic radicals such as $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2CF_3$, $-CHFCF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, and $-CH_2CH_2F$, with $-CF_3$ being preferred.

The term, "(Acidic Group)" means a carbon atom linked organic group that acts as a proton donor capable of hydrogen bonding. Illustrative of an (Acidic Group) is a group selected from the following:

-C(O)OH,

-5-tetrazolyl,



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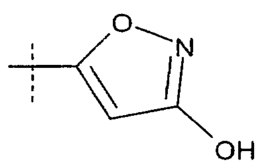

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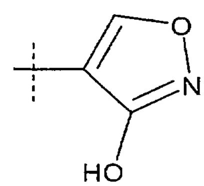

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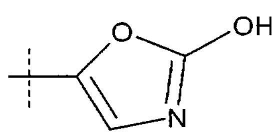

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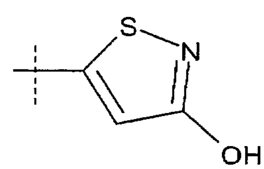

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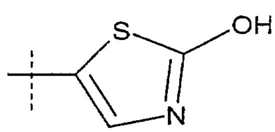

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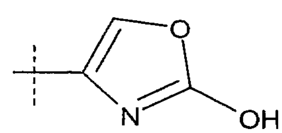

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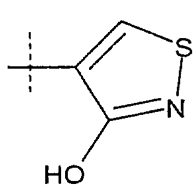

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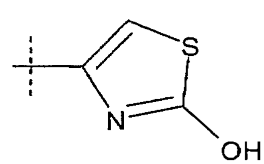

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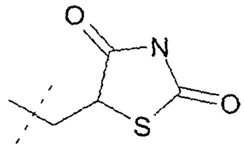
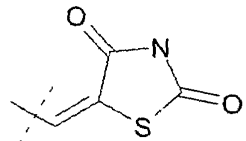
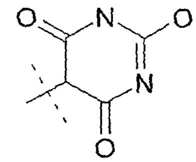
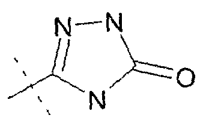
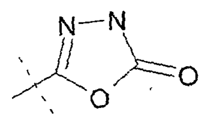
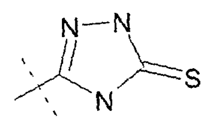
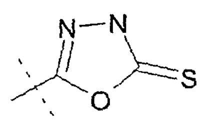
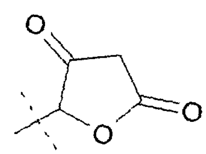
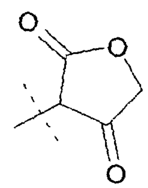
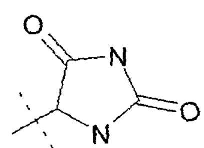
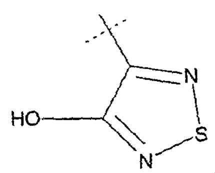
,
,
,

,
,
,

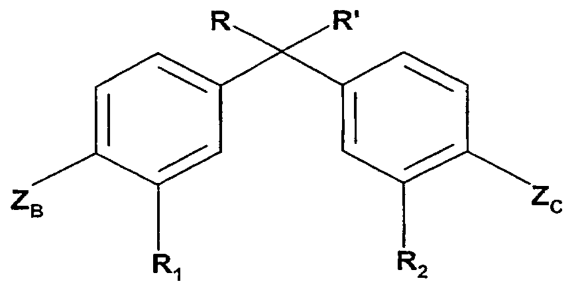
,
,
,

,

.

Compounds of the Invention:

The compounds of the invention with vitamin receptor modulating (VDRM) activities are represented by formula (I) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



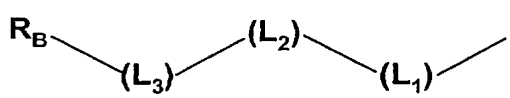
(I)

wherein;

R and R' are independently C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, or together R and R' form a substituted or unsubstituted, saturated or unsaturated carbocyclic ring having from 3 to 8 carbon atoms;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, -O-C_1-C_5 alkyl, -S-C_1-C_5 alkyl, -O-C_1-C_5 fluoroalkyl, -CN, -NO_2, acetyl, -S-C_1-C_5 fluoroalkyl, C_2-C_5 alkenyl, C_3-C_5 cycloalkyl, and C_3-C_5 cycloalkenyl;

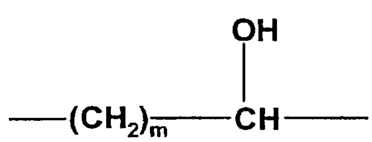
Z_B is a group represented by the formula:



wherein

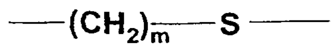
-(L_1), -(L_2)-, and -(L_3)- is each a divalent linking groups independently selected from the group consisting of

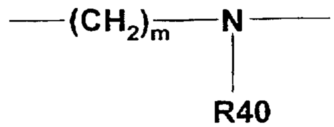
a bond ,

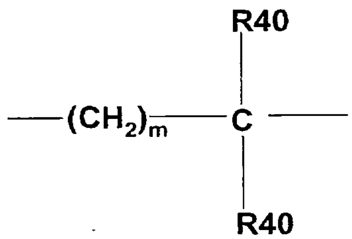


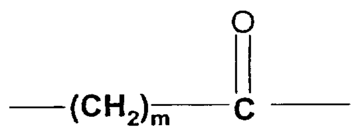
,

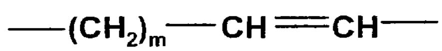
$—(CH_2)_m—O—$,

 ,

 ,

 ,

 ,

 , and

 ,

where m is 0, 1, or 2, and each R40 is independently hydrogen, C_1-C_5 alkyl, or C_1-C_5 fluoroalkyl;

R_B is a branched C_3-C_5 alkyl;

Z_C is a carbon atom linked group selected from

-CO_2H,

-CO_2Me,

-CO_2Et,

-$C(O)CH_2S(O)Me$,

-$C(O)CH_2S(O)Et$,

-$C(O)CH_2S(O)_2Me$,

-$C(O)CH_2S(O)_2Et$,

-$C(O)CH_2CH_2S(O)Me$,

-$C(O)CH_2CH_2S(O)Et$,

-$C(O)CH_2CH_2S(O)_2Me$,

-$C(O)CH_2CH_2S(O)_2Et$,

-$C(O)CH(Me)CH_2CO_2H$,

$-C(O)CH(Me)CH_2CO_2Me$,

$-C(O)CH(Me)CH_2CO_2Et$,

$-C(O)CH(Me)CH_2CO_2iPr$,

$-C(O)CH(Me)CH_2CO_2tBu$,

$-C(O)CH(Me)CH(Me)CO_2H$,

$-C(O)CH(Me)CH(Me)CO_2Me$,

$-C(O)CH(Me)CH(Me)CO_2Et$,

$-C(O)CH(Me)CH(Me)CO_2iPr$,

$-C(O)CH(Me)CH(Me)CO_2tBu$,

$-C(O)CH(Me)C(Me)_2CO_2H$,

$-C(O)CH(Me)C(Me)_2CO_2Me$,

$-C(O)CH(Me)C(Me)_2CO_2Et$,

$-C(O)CH(Me)C(Me)_2CO_2iPr$,

$-C(O)CH(Me)C(Me)_2CO_2tBu$,

$-C(O)CH(Me)CH(Et)CO_2H$,

$-C(O)CH(Me)CH(Et)CO_2Me$,

$-C(O)CH(Me)CH(Et)CO_2Et$,

$-C(O)CH(Me)CH(Et)CO_2iPr$,

$-C(O)CH(Me)CH(Et)CO_2tBu$,

$-C(O)C(O)OH$,

$-C(O)C(O)NH_2$,

$-C(O)C(O)NHMe$,

$-C(O)C(O)NMe_2$,

-C(O)NH$_2$,

-C(O)NMe$_2$,

-C(O)NH-CH$_2$-C(O)OH,

-C(O)NH-CH$_2$-C(O)OMe,

-C(O)NH-CH$_2$-C(O)OEt,

-C(O)NH-CH$_2$-C(O)OiPr,

-C(O)NH-CH$_2$-C(O)OtBu,

-C(O)NH-CH(Me)-C(O)OH,

-C(O)NH-CH(Me)-C(O)OMe,

-C(O)NH-CH(Me)-C(O)OEt,

-C(O)NH-CH(Me)-C(O)iPr,

-C(O)NH-CH(Me)-C(O)tBu,

-C(O)NH-CH(Et)-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OMe,

-C(O)NH-C(Me)$_2$-C(O)OEt,

-C(O)NH-C(Me)$_2$-C(O)iPr,

-C(O)NH-C(Me)$_2$-C(O)tBu,

-C(O)NH-CMe(Et)-C(O)OH,

-C(O)NH-CH(F)-C(O)OH,

-C(O)NH-CH(CF$_3$)-C(O)OH,

-C(O)NH-CH(OH)-C(O)OH,

-C(O)NH-CH(cyclopropyl)-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OH,

-C(O)NH-CF(Me)-C(O)OH,

-C(O)NH-C(Me)(CF$_3$)-C(O)OH,

-C(O)NH-C(Me)(OH)-C(O)OH,

-C(O)NH-C(Me)(cyclopropyl)CO$_2$H

-C(O)NMe-CH$_2$-C(O)OH,

-C(O)NMe-CH$_2$-C(O)OMe,

-C(O)NMe-CH$_2$-C(O)OEt,

-C(O)NMe-CH_2-C(O)OiPr,

-C(O)NMe-CH_2-C(O)tBu,

-C(O)NMe-CH_2-C(O)OH,

-C(O)NMe-CH(Me)-C(O)OH,

-C(O)NMe-CH(F)-C(O)OH,

-C(O)NMe-CH(CF_3)-C(O)OH,

-C(O)NMe-CH(OH)-C(O)OH,

-C(O)NMe-CH(cyclopropyl)-C(O)OH,

-C(O)NMe-$C(Me)_2$-C(O)OH,

-C(O)NMe-CF(Me)-C(O)OH,

-C(O)NMe-C(Me)(CF_3)-C(O)OH,

-C(O)NMe-C(Me)(OH)-C(O)OH,

-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH,

-C(O)NHS(O)Me,

-C(O)$NHSO_2$Me,

-C(O)-NH-5-tetrazolyl,

-C(O)NHS(O)Me,

-C(O)NHS(O)Et,

-C(O)$NHSO_2$Me,

-C(O)$NHSO_2$Et,

-C(O)NHS(O)iPr,

-C(O)$NHSO_2$iPr,

-C(O)NHS(O)tBu,

-C(O)$NHSO_2$tBu,

-C(O)$NHCH_2$S(O)Me,

-C(O)$NHCH_2$S(O)Et,

-C(O)$NHCH_2SO_2$Me,

-C(O)$NHCH_2SO_2$Et,

-C(O)$NHCH_2CH_2$S(O)Me,

-C(O)$NHCH_2CH_2$S(O)Et,

-C(O)$NHCH_2CH_2SO_2$Me,

-C(O)$NHCH_2CH_2SO_2$Et,

-C(O)N(Me)S(O)Me,

-C(O)N(Me)SO_2Me,

-C(O)-N(Me)-5-tetrazolyl,

-C(O)N(Me)S(O)Me,

-C(O)N(Me)S(O)Et,

-C(O)N(Me)SO_2Me,

-C(O)N(Me)SO_2Et,

-C(O)N(Me)S(O)iPr,

-C(O)N(Me))SO_2iPr,

-C(O)N(Me))S(O)tBu,

-C(O)N(Me)SO_2tBu,

-C(O)N(Me)CH_2S(O)Me,

-C(O)N(Me)CH_2S(O)Et,

-C(O)N(Me)CH_2SO_2Me,

-C(O)N(Me)CH_2SO_2Et,

-C(O)N(Me)CH_2CH_2S(O)Me,

-C(O)N(Me)CH_2CH_2S(O)Et,

-C(O)N(Me)$CH_2CH_2SO_2$Me,

-C(O)N(Me)$CH_2CH_2SO_2$Et,

-CH_2CO_2H,

-CH_2-5-tetrazolyl,

-CH_2CO_2Me,

-CH_2CO_2Et,

-CH_2NHS(O)Me,

-CH_2NHS(O)Et,

-CH_2NHSO_2Me,

-CH_2NHSO_2Et,

-CH_2NHS(O)iPr,

-CH_2NHSO_2iPr,

-CH_2NHS(O)tBu,

-CH_2NHSO_2tBu,

-$CH_2NHCH_2CH_2SO_2CH_3$,

$-CH_2NH(CH_2CO_2H)$,

$-CH_2N(C(O)Me)(CH_2CO_2H)$,

$-CH_2$-N-pyrrolidin-2-one,

$-CH_2$-(1-methylpyrrolidin-2-one-3-yl),

$-CH_2S(O)Me$,

$-CH_2S(O)Et$,

$-CH_2S(O)_2Me$,

$-CH_2S(O)_2Et$,

$-CH_2S(O)iPr$,

$-CH_2S(O)_2iPr$,

$-CH_2S(O)tBu$,

$-CH_2S(O)_2tBu$,

$-CH_2CO_2H$, $CH_2C(O)NH_2$,

$-CH_2C(O)NMe_2$,

$-CH_2C(O)NHMe$,

$-CH_2C(O)$-N-pyrrolidine,

$-CH_2S(O)_2Me$, $CH_2S(O)Me$,

$-CH(OH)\ CO_2H$,

$-CH(OH)C(O)NH_2$,

$-CH(OH)C(O)NHMe$,

$-CH(OH)C(O)NMe_2$,

$-CH(OH)C(O)NEt_2$,

$-CH_2CH_2CO_2H$,

$-CH_2CH_2CO_2Me$,

$-CH_2CH_2CO_2Et$,

$-CH_2CH_2C(O)NH_2$,

$-CH_2CH_2C(O)NHMe$,

$-CH_2CH_2C(O)NMe_2$,

$-CH_2CH_2$-5-tetrazolyl,

$-CH_2CH_2S(O)_2Me$,

$-CH_2CH_2S(O)Me$,

$-CH_2CH_2S(O)_2Et$,

-$CH_2CH_2S(O)$ Et,

-$CH_2CH_2S(O)$iPr,

-$CH_2CH_2S(O)_2$iPr,

-$CH_2CH_2S(O)$tBu,

-$CH_2CH_2S(O)_2$tBu,

-$CH_2CH_2S(O)NH_2$,

-$CH_2CH_2S(O)NHMe$,

-$CH_2CH_2S(O)NMe_2$,

-$CH_2CH_2S(O)_2NH_2$,

-$CH_2CH_2S(O)_2NHMe$

-$CH_2CH_2S(O)_2NMe_2$,

-$CH_2CH_2CH_2S(O)Me$,

-$CH_2CH_2CH_2S(O)Et$,

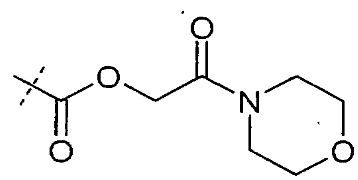
-$CH_2CH_2CH_2S(O)_2Me$,

-$CH_2CH_2CH_2S(O)_2Et$,

-C(O)OH,

-5-tetrazolyl,

-C(O)-N(Me)-5-tetrazolyl,



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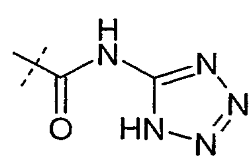

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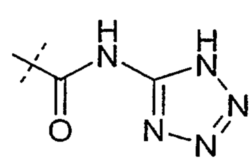

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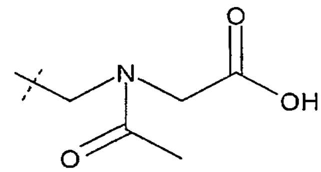

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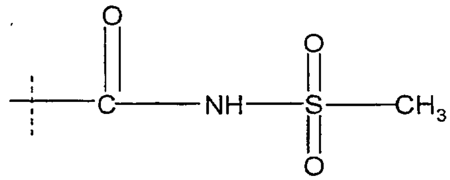

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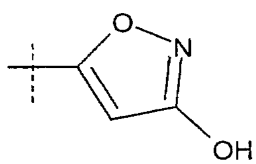

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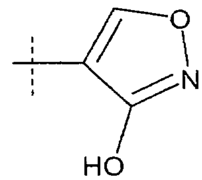

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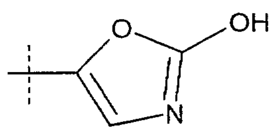

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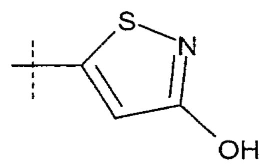

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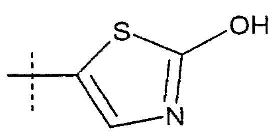

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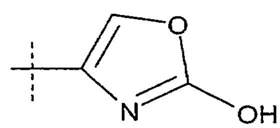

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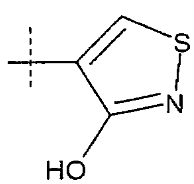

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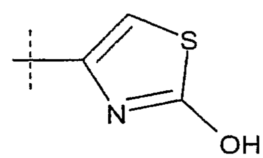

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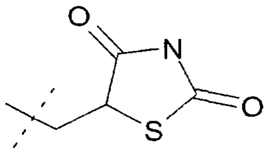
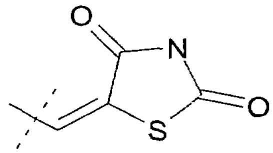
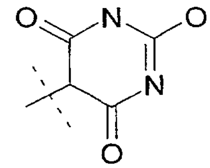
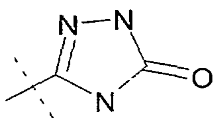
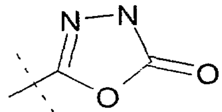
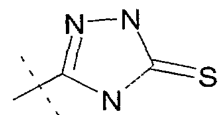
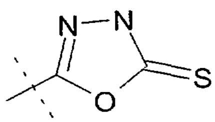
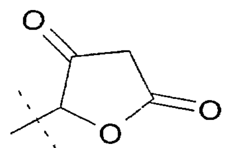
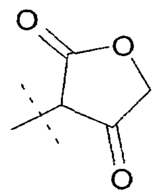
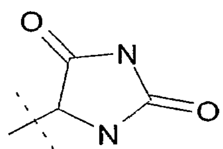
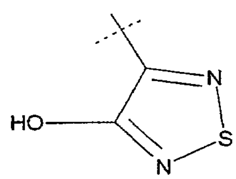
 ,  ,  ,

 ,  ,  ,

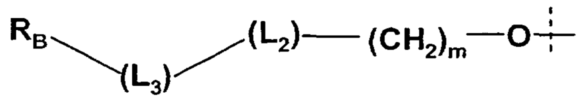
 ,  ,  ,

 ,

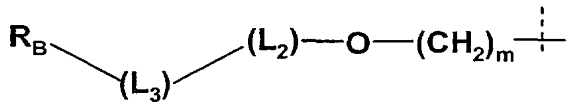


-1,3,4-oxadiazolin-2-one-5-yl,
-imidazolidine-2,4-dione-5-yl,
-isoxazol-3-ol-yl, or
-1,3,4-oxadiazolin-2-thione-5-yl.

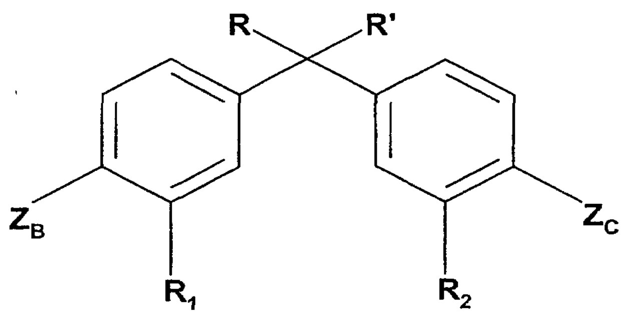
In the preceding formula (I) the divalent linking groups -(L1)- and -(L2)- and -(L3)- are understood (in the case of those having more than one substituent) to be oriented in either direction, for example, where divalent linker (L1) has the identity -$(CH_2)_m$-O- , it may be configured:



or



Preferred compounds of the invention with VDR modulating activities are represented by formula (I) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



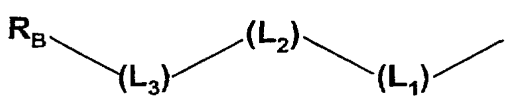
(I)

wherein;

R and R' are independently methyl, ethyl, propyl, or 1-methylethyl;

R_1 and R_2 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

Z_B is a branched alkyl terminated group represented by the formula:



R_B is 1-methylethyl; 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; 2,2-dimethylpropyl; 3-methyl-3-hydroxy-4,4-dimethylpentyl; 3-methyl-3-hydroxy-4,4-dimethylpentenyl; 3-methyl-3-hydroxy-4,4-dimethylpentyl; 3-ethyl-3-hydroxy-4,4-dimethylpentynyl; 3-ethyl-3-hydroxy-4,4-dimethylpentenyl; or 3-ethyl-3-hydroxy-4,4-dimethylpentynyl;

(L_1) and (L_2) and (L_3) are independently divalent linking groups where

L_1 is –O-, –CH_2- , -CHOH-, –CH(Me)- , -C(O)-, or -C(Me)OH- ;

L_2 is -CH_2- ,, -CHOH-, –CH(Me)- , -C(O)-, or -C(Me)OH- ; or

L_1 and L_2 taken together is the group

—CH_2—CH_2— ,

—CH=CH— , or

—C≡C— ;

L_3 is a bond, -CH_2- , -CHOH- , –CH(Me)- -C(O)-, or -C(Me)OH- ;

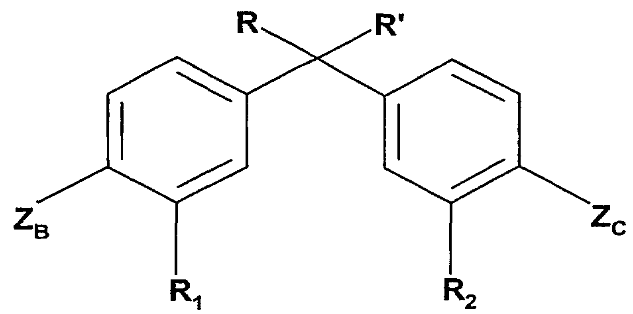
Z_C is a group selected from

-C(O)CH_2S(O)Me,
-C(O)CH_2S(O)Et,
-C(O)CH_2S$(O)_2$Me,
-C(O)CH_2S$(O)_2$Et,
-C(O)CH_2CH_2S(O)Me,
-C(O)CH_2CH_2S(O)Et,
-C(O)CH_2CH_2S$(O)_2$Me,
-C(O)CH_2CH_2S$(O)_2$Et,
-C(O)CH(Me)CH_2CO_2H,
-C(O)CH(Me)CH_2CO_2Me,
-C(O)CH(Me)CH_2CO_2Et,
-C(O)CH(Me)CH_2CO_2iPr,
-C(O)CH(Me)CH_2CO_2tBu,
-C(O)CH(Me)CH(Me)CO_2H,
-C(O)CH(Me)CH(Me)CO_2Me,
-C(O)CH(Me)CH(Me)CO_2Et,
-C(O)CH(Me)CH(Me)CO_2iPr,
-C(O)CH(Me)CH(Me)CO_2tBu,
-C(O)CH(Me)C(Me) $_2CO_2$H,
-C(O)CH(Me)C(Me) $_2CO_2$Me,

-C(O)CH(Me)C(Me) $_2CO_2$Et,
-C(O)CH(Me)C(Me) $_2CO_2$iPr,
-C(O)CH(Me)C(Me) $_2CO_2$tBu,
-C(O)CH(Me)CH(Et)CO_2H,
-C(O)CH(Me)CH(Et)CO_2Me,
-C(O)CH(Me)CH(Et)CO_2Et,
-C(O)CH(Me)CH(Et)CO_2iPr,
-C(O)CH(Me)CH(Et)CO_2tBu,
-C(O)C(O)OH,
-C(O)C(O)NH_2,
-C(O)C(O)NHMe,
-C(O)C(O)NMe_2,
-C(O)NH_2,
-C(O)NMe_2,
-C(O)NH-CH_2-C(O)OH,
-C(O)NH-CH_2-C(O)OMe,
-C(O)NH-CH_2-C(O)OEt,
-C(O)NH-CH_2-C(O)OiPr,
-C(O)NH-CH_2-C(O)OtBu,
-C(O)NH-CH(Me)-C(O)OH,
-C(O)NH-CH(Me)-C(O)OMe,
-C(O)NH-CH(Me)-C(O)OEt,
-C(O)NH-CH(Me)-C(O)iPr,
-C(O)NH-CH(Me)-C(O)tBu,
-C(O)NH-CH(Et)-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OMe,
-C(O)NH-C$(Me)_2$-C(O)OEt,
-C(O)NH-C$(Me)_2$-C(O)iPr,
-C(O)NH-C$(Me)_2$-C(O)tBu,
-C(O)NH-CMe(Et)-C(O)OH,
-C(O)NH-CH(F)-C(O)OH,

-C(O)NH-CH(CF_3)-C(O)OH,
-C(O)NH-CH(OH)-C(O)OH,
-C(O)NH-CH(cyclopropyl)-C(O)OH,
-C(O)NH-C($Me)_2$-C(O)OH,
-C(O)NH-C($Me)_2$-C(O)OH,
-C(O)NH-CF(Me)-C(O)OH,
-C(O)NH-C(Me)(CF_3)-C(O)OH,
-C(O)NH-C(Me)(OH)-C(O)OH,
-C(O)NH-C(Me)(cyclopropyl)CO_2H,
-C(O)NMe-CH_2-C(O)OH,
-C(O)NMe-CH_2-C(O)OMe,
-C(O)NMe-CH_2-C(O)OEt,
-C(O)NMe-CH_2-C(O)OiPr,
-C(O)NMe-CH_2-C(O)tBu,
-C(O)NMe-CH(Me)-C(O)OH,
-C(O)NMe-CH(F)-C(O)OH,
-C(O)NMe-CH(CF_3)-C(O)OH,
-C(O)NMe-CH(OH)-C(O)OH,
-C(O)NMe-CH(cyclopropyl)-C(O)OH,
-C(O)NMe-C($Me)_2$-C(O)OH,
-C(O)NMe-CF(Me)-C(O)OH,
-C(O)NMe-C(Me)(CF_3)-C(O)OH,
-C(O)NMe-C(Me)(OH)-C(O)OH,
-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH, or
-C(O)-N(Me)-5-tetrazolyl.

Other preferred compounds of the invention are those represented by formula (I) or a pharmaceutically acceptable salt or a prodrug derivative thereof:



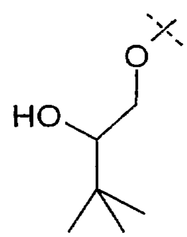
(I)

wherein;

R and R' are independently methyl or ethyl;

R_1 and R_2 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, or cyclopropyl;

Z_B is a branched alkyl terminated selected from the formulae:



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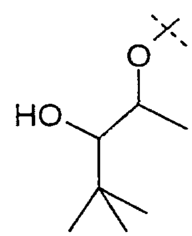

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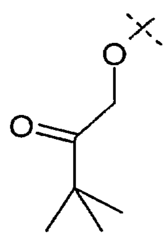

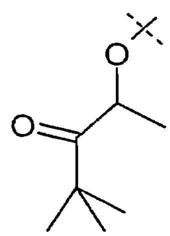

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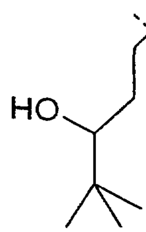
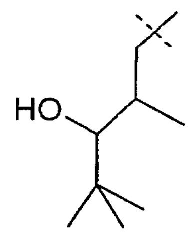
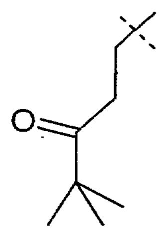
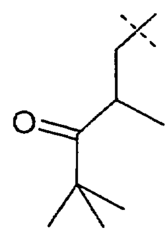
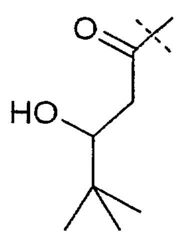
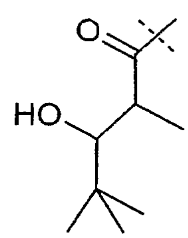
 ,

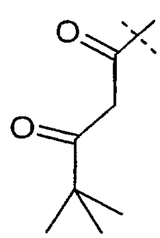
 ,

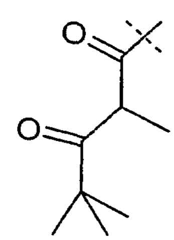


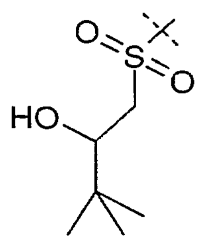
 ;

 ,

 ,



 ,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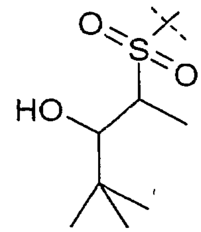
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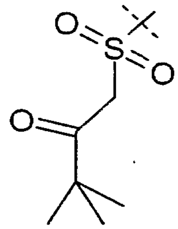
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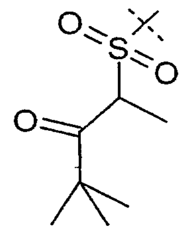

;

Z_C is selected from

-C(O)NH_2,
-C(O)NMe_2,
-C(O)NH-CH_2-C(O)OH,
-C(O)NH-CH_2-C(O)OMe,
-C(O)NH-CH_2-C(O)OEt,
-C(O)NH-CH_2-C(O)OiPr,
-C(O)NH-CH_2-C(O)OtBu,
-C(O)NH-CH(Me)-C(O)OH,
-C(O)NH-CH(Me)-C(O)OMe,
-C(O)NH-CH(Me)-C(O)OEt,
-C(O)NH-CH(Me)-C(O)iPr,
-C(O)NH-CH(Me)-C(O)tBu,
-C(O)NH-CH(Et)-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OMe,
-C(O)NH-$C(Me)_2$-C(O)OEt,

-C(O)NH-C(Me)$_2$-C(O)iPr,

-C(O)NH-C(Me)$_2$-C(O)tBu,

-C(O)NH-CMe(Et)-C(O)OH,

-C(O)NH-CH(F)-C(O)OH,

-C(O)NH-CH(CF$_3$)-C(O)OH,

-C(O)NH-CH(OH)-C(O)OH,

-C(O)NH-CH(cyclopropyl)-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OH,

-C(O)NH-C(Me)$_2$-C(O)OH,

-C(O)NH-CF(Me)-C(O)OH,

-C(O)NH-C(Me)(CF$_3$)-C(O)OH,

-C(O)NH-C(Me)(OH)-C(O)OH,

-C(O)NH-C(Me)(cyclopropyl)CO$_2$H,

-C(O)NMe-CH$_2$-C(O)OH,

-C(O)NMe-CH$_2$-C(O)OMe,

-C(O)NMe-CH$_2$-C(O)OEt,

-C(O)NMe-CH$_2$-C(O)OiPr,

-C(O)NMe-CH$_2$-C(O)tBu,

-C(O)NMe-CH(Me)-C(O)OH,

-C(O)NMe-CH(F)-C(O)OH,

-C(O)NMe-CH(CF$_3$)-C(O)OH,

-C(O)NMe-CH(OH)-C(O)OH,

-C(O)NMe-CH(cyclopropyl)-C(O)OH,

-C(O)NMe-C(Me)$_2$-C(O)OH,

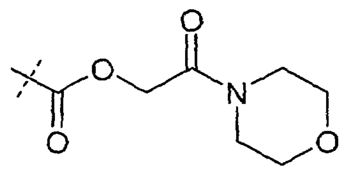
-C(O)NMe-CF(Me)-C(O)OH,

-C(O)NMe-C(Me)(CF$_3$)-C(O)OH,

-C(O)NMe-C(Me)(OH)-C(O)OH,

-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH,

-C(O)-N(Me)-5-tetrazolyl,



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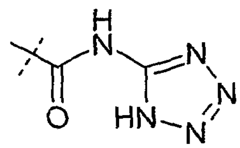

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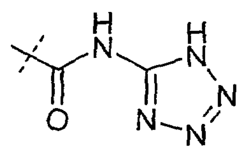

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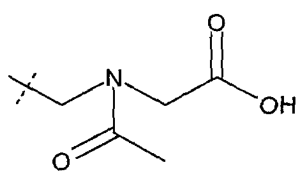

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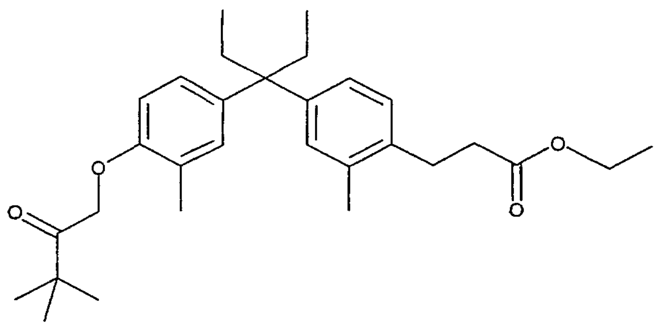
Particularly preferred is a compound or a pharmaceutically acceptable salt or ester prodrug derivative thereof represented by structural formulae (AA) to(DB) as follows:

AA)



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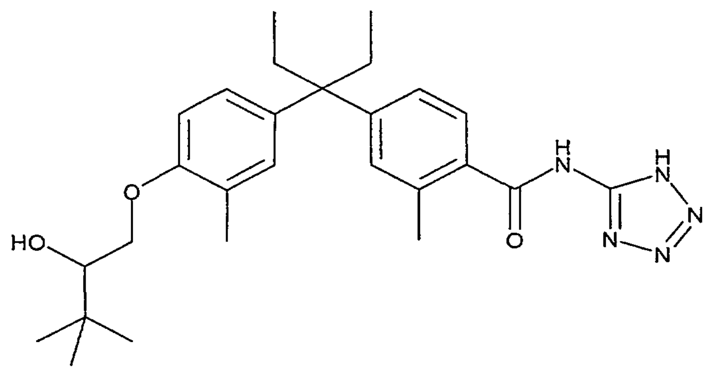
AF)



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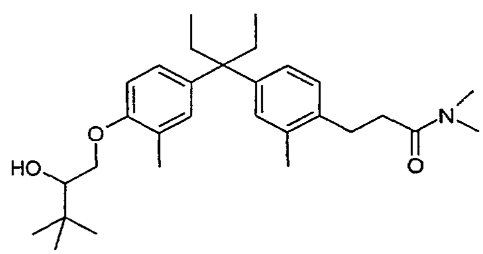
AJ)



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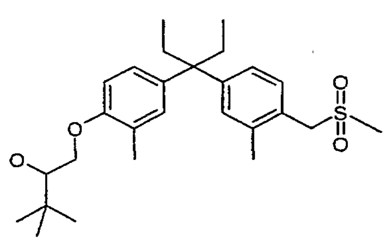

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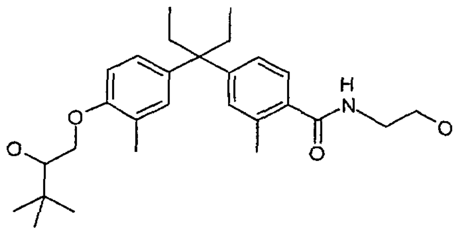
AR)



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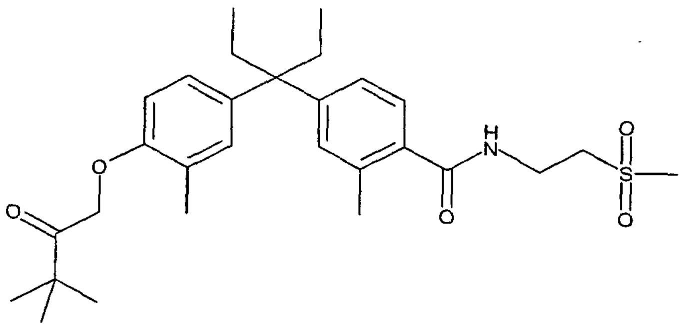
AS)



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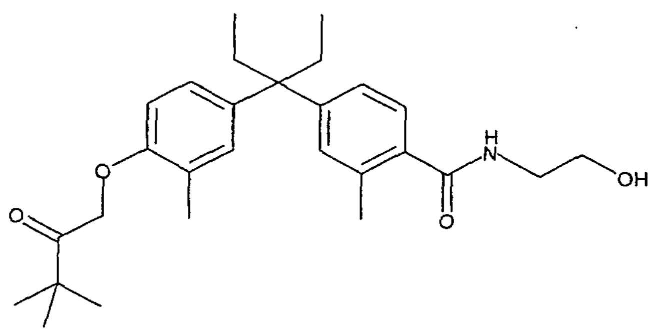

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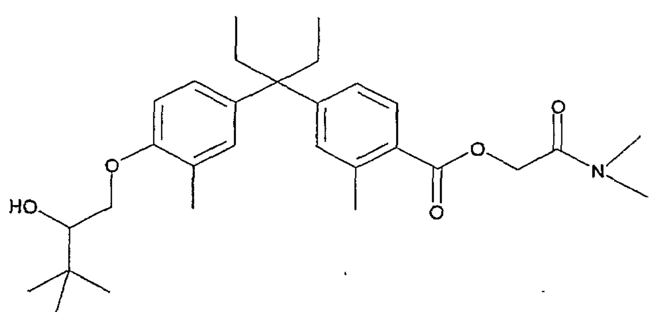

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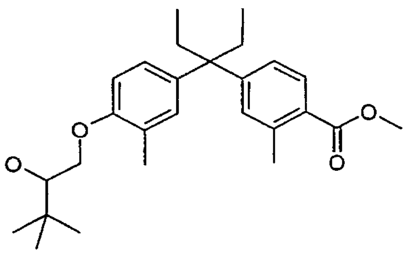
AZ)



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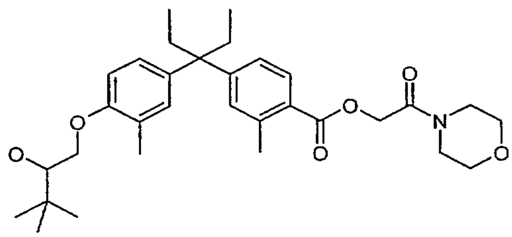
BA)



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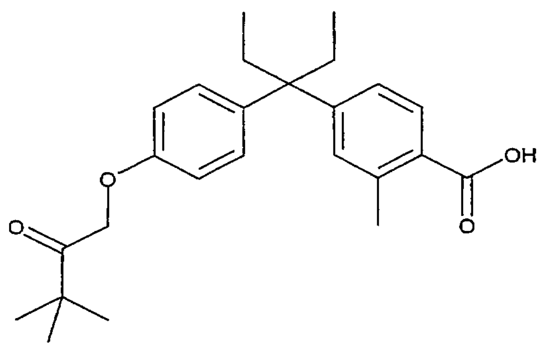

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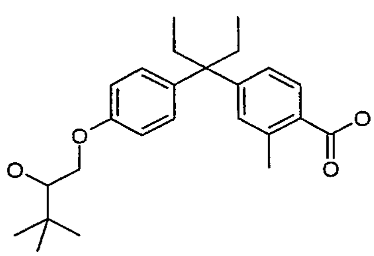

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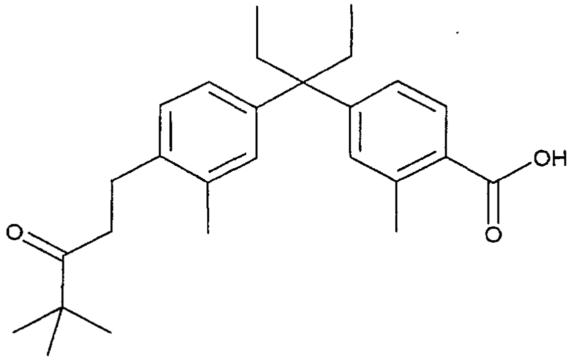

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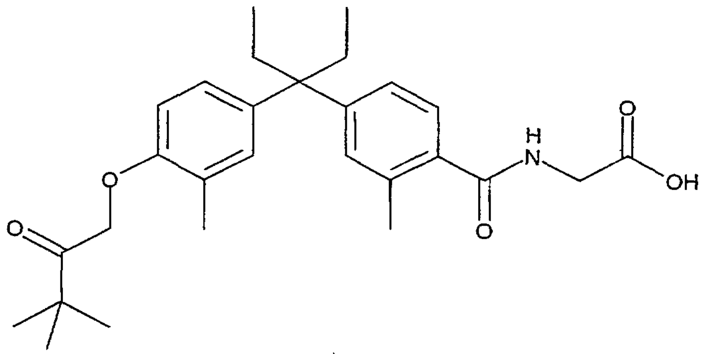

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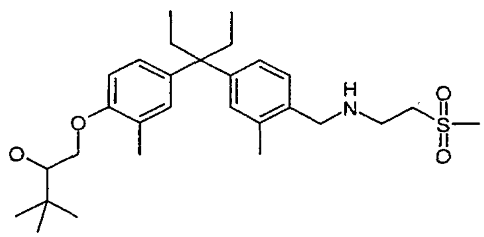

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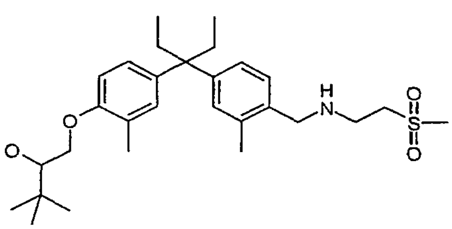

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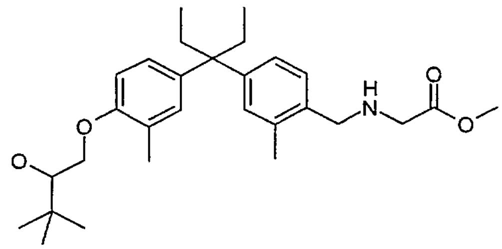

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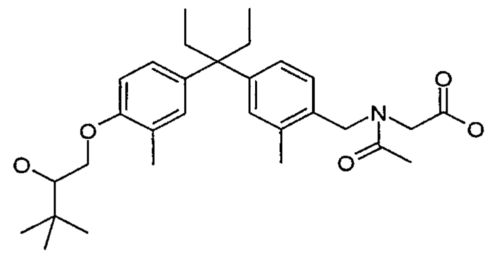

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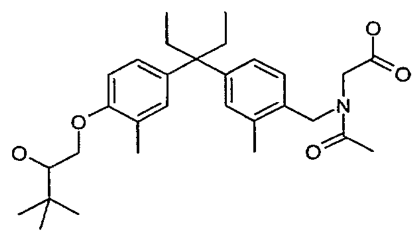

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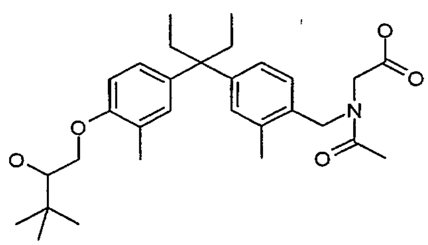

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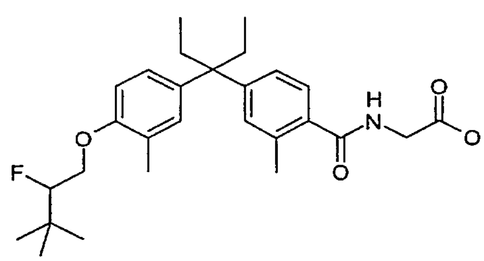
CC)



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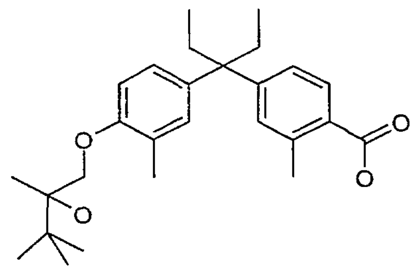

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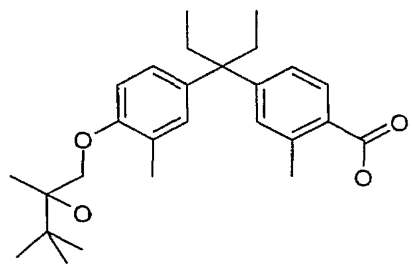

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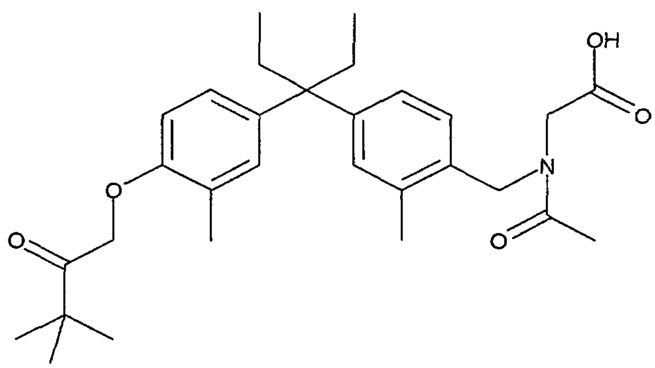

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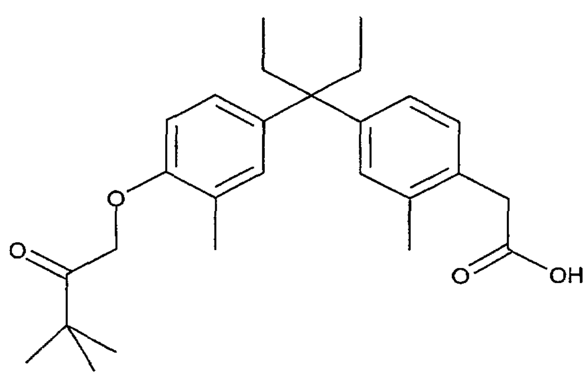

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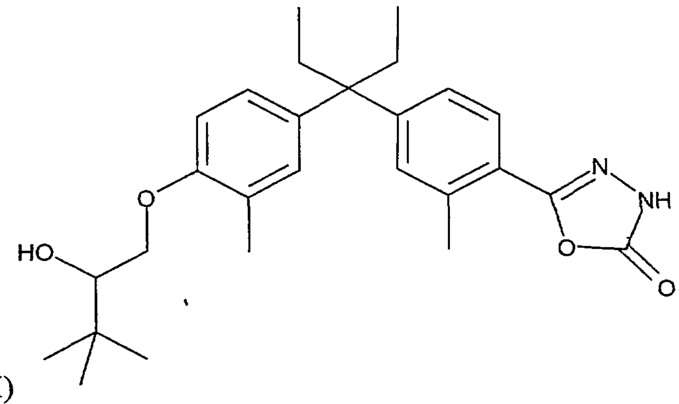
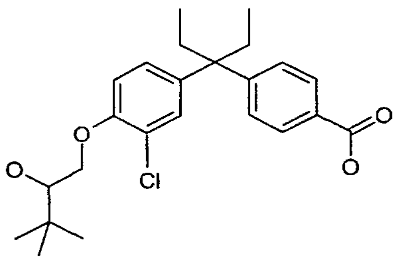


CM) ,

CN)



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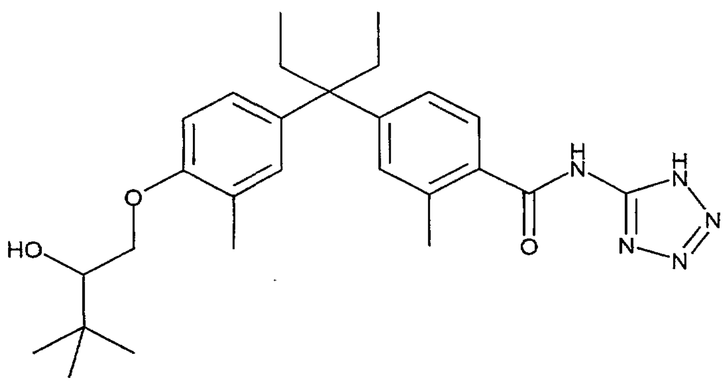
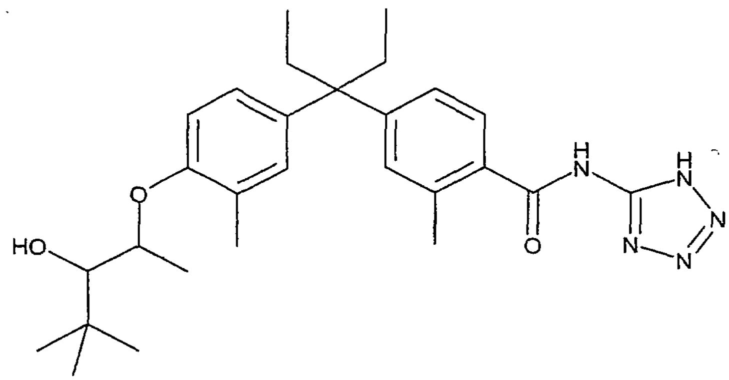


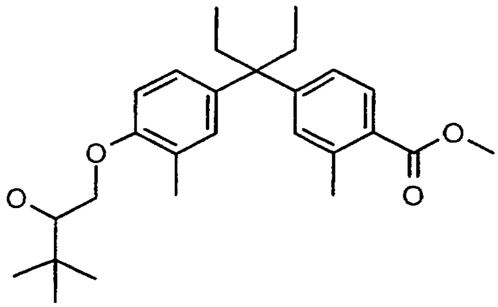
, or

DB)

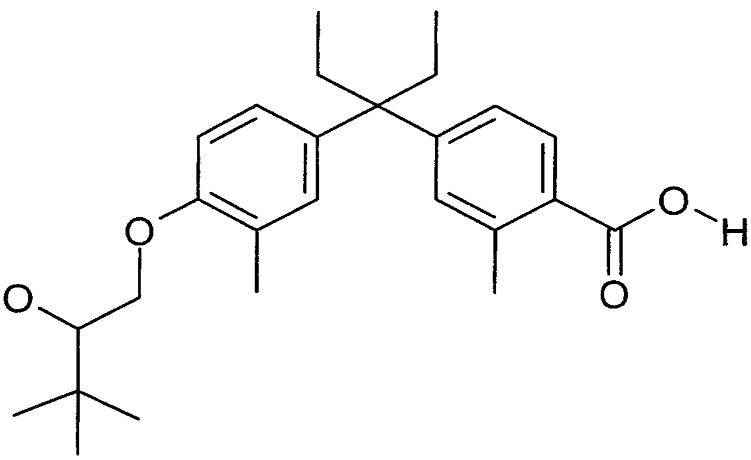


Other particularly preferred compounds of the invention are those shown by the structural formulae C-1 to C-54 set out below. Pharmaceutically acceptable salts for prodrug derivatives of these compounds are also preferred.

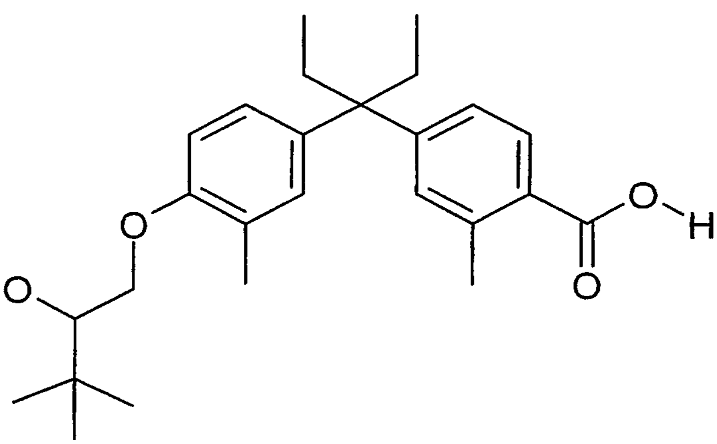
C-1)



C-2)



C-3)



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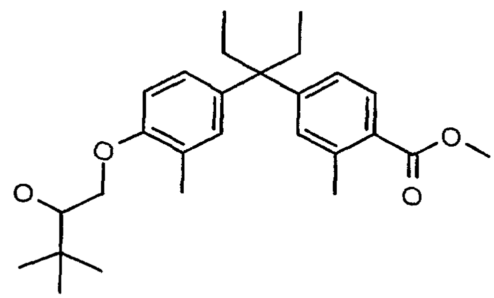

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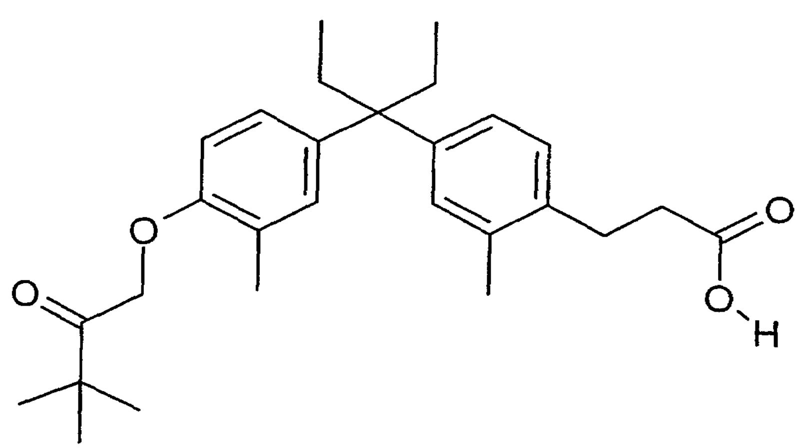
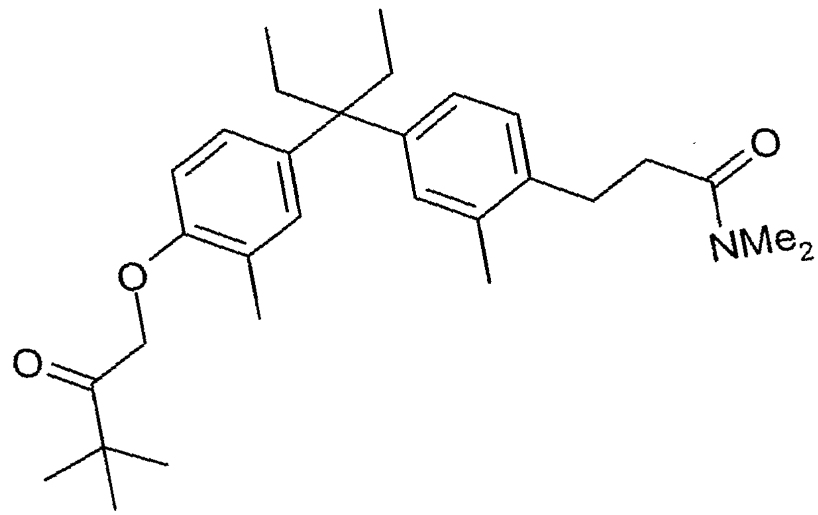
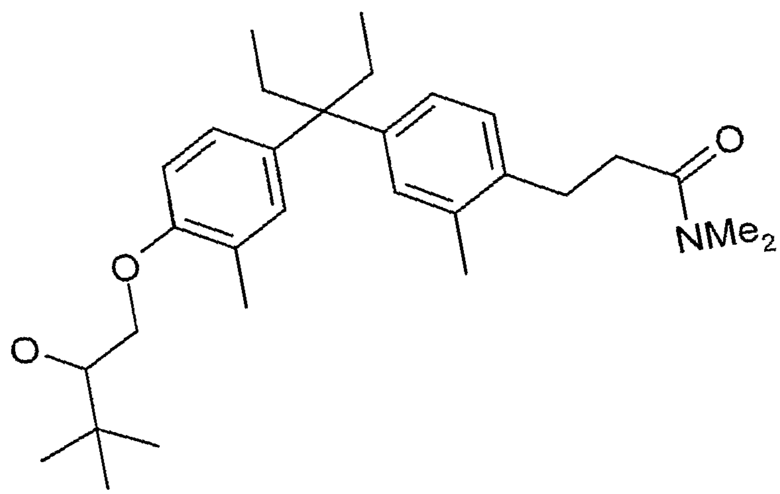


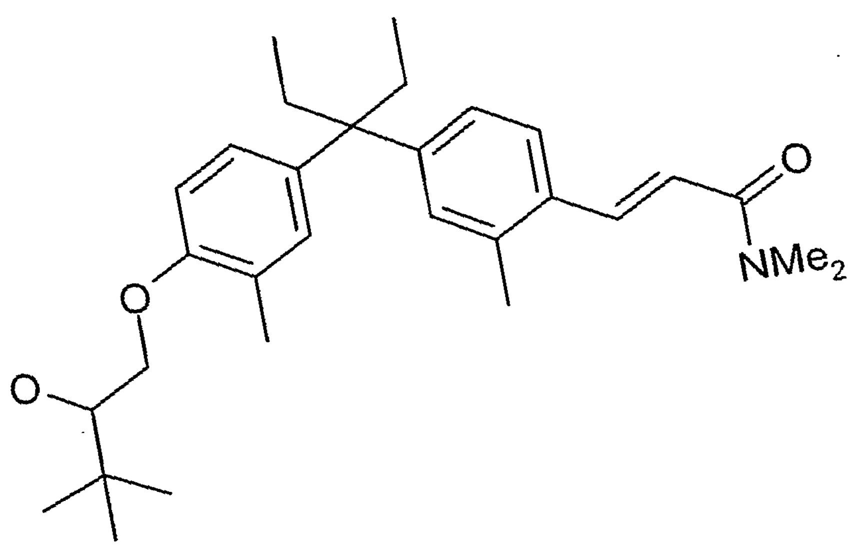
C-7)



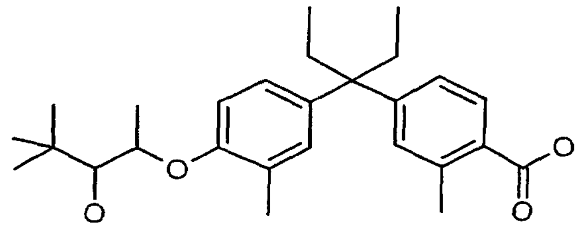
C-8)



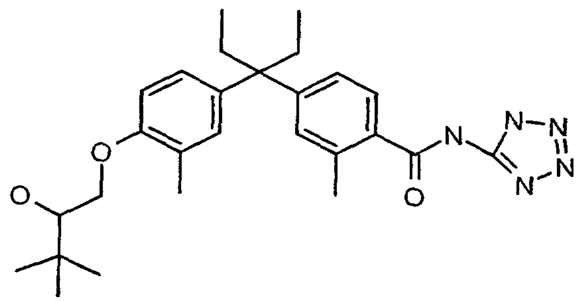
C-9)



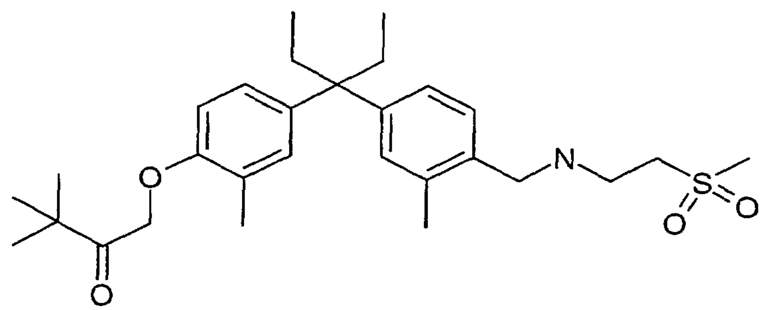
C-10)



C-12)



C-13)



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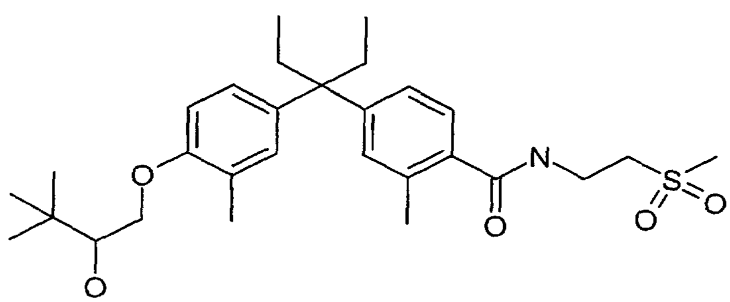

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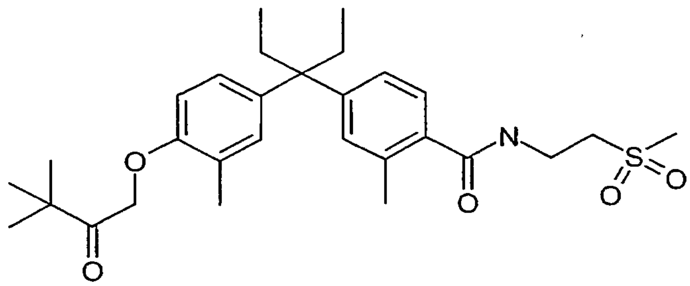

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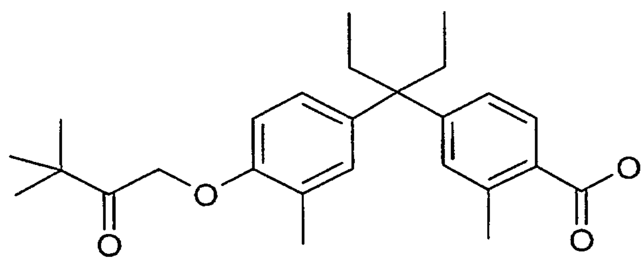

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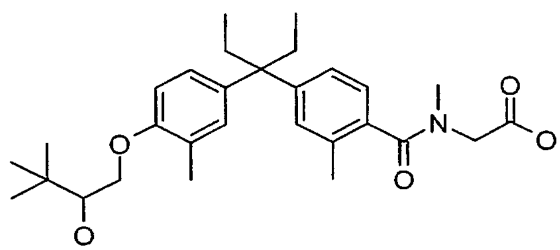

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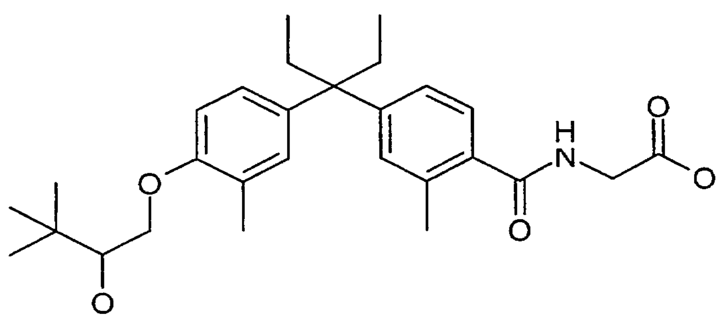

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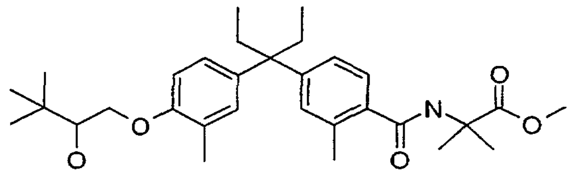

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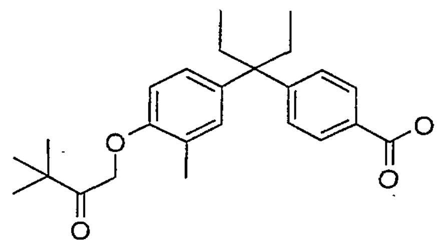

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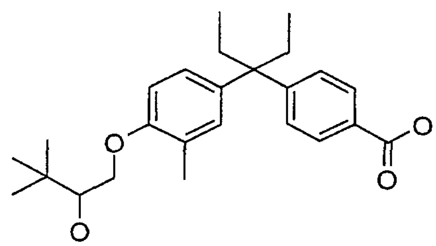
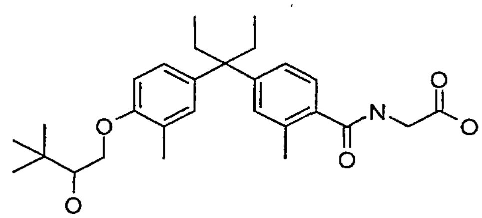
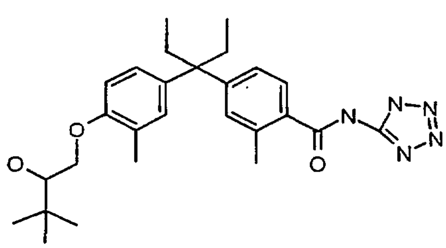


C-25)



C-26)



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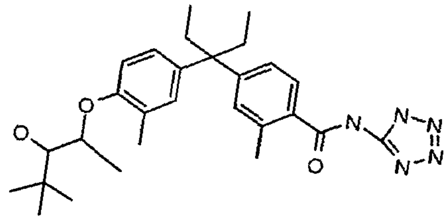

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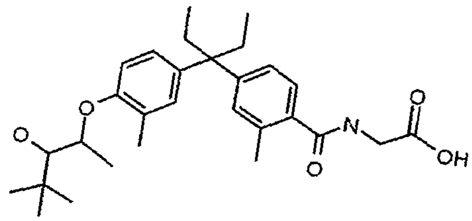

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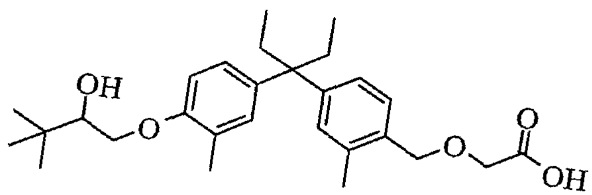

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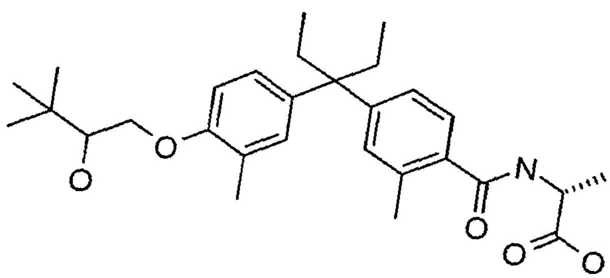

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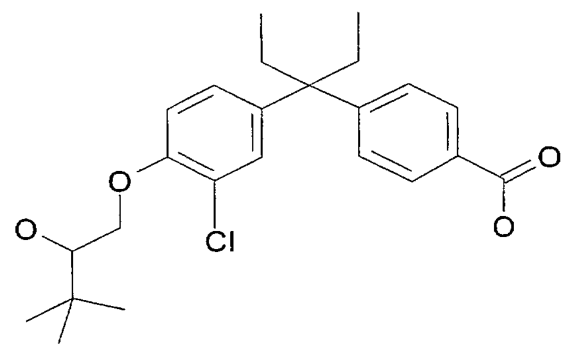

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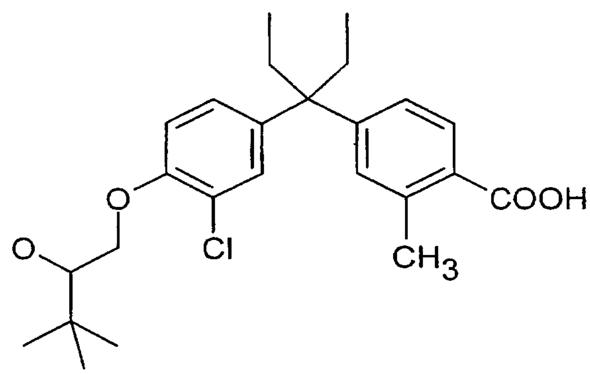

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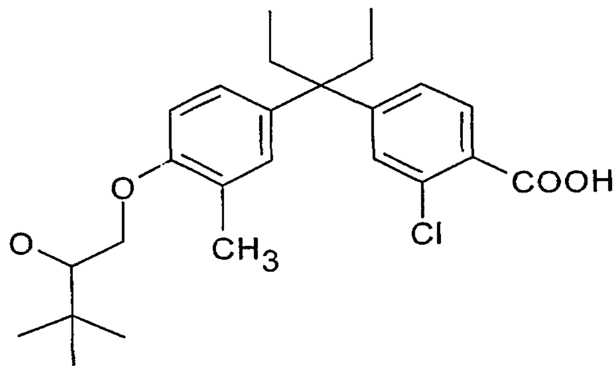

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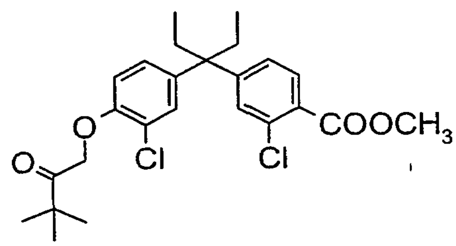

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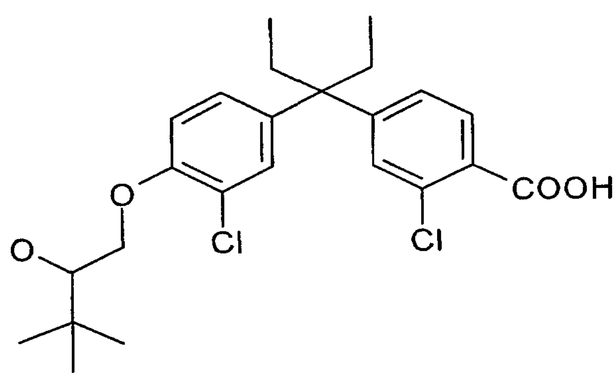
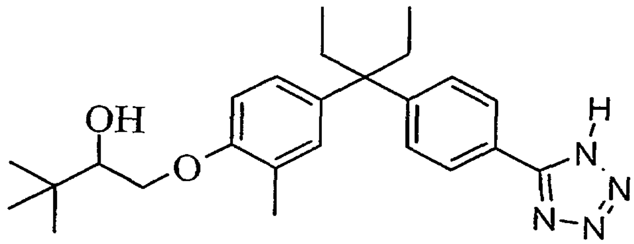


C-48)



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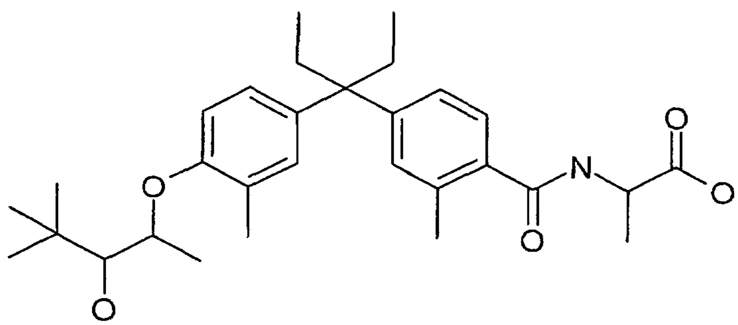
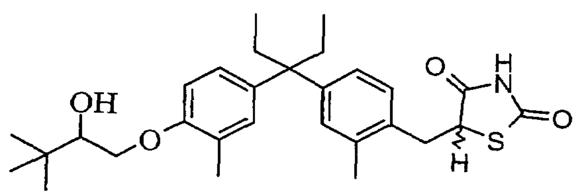
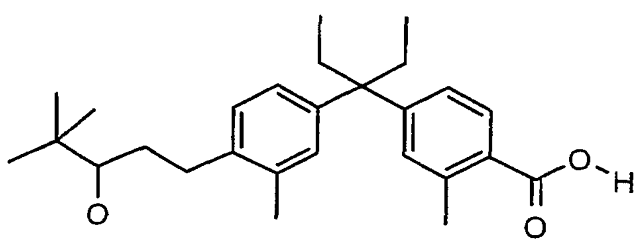


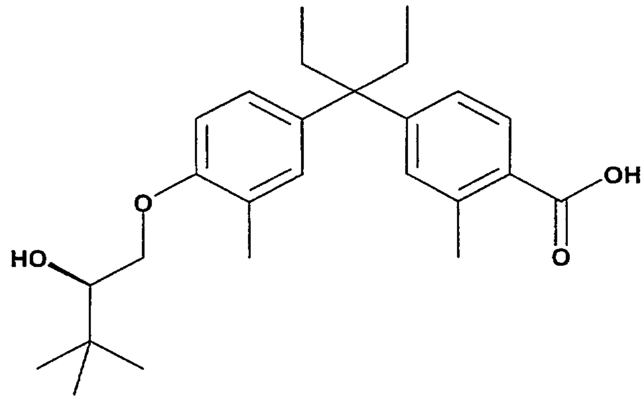
C-54)



C-55)



Most preferred are the individual enantiomers or a mixture of enantiomers represented by the formulae:



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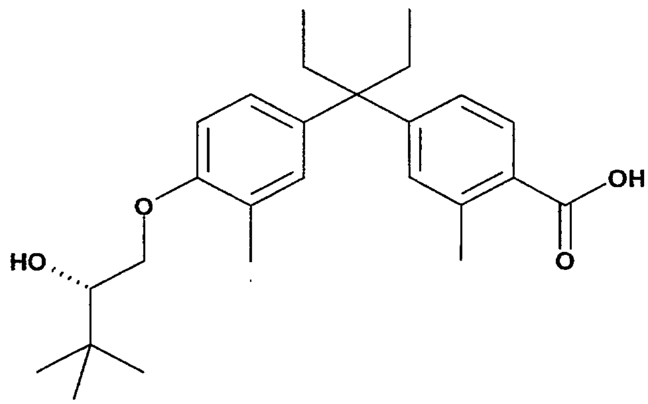

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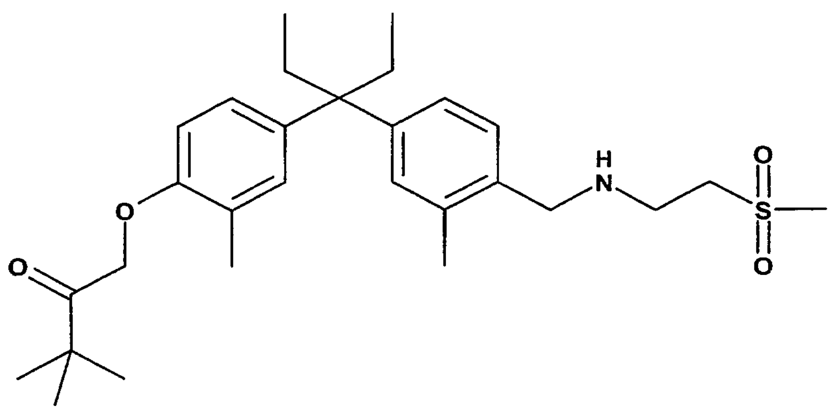
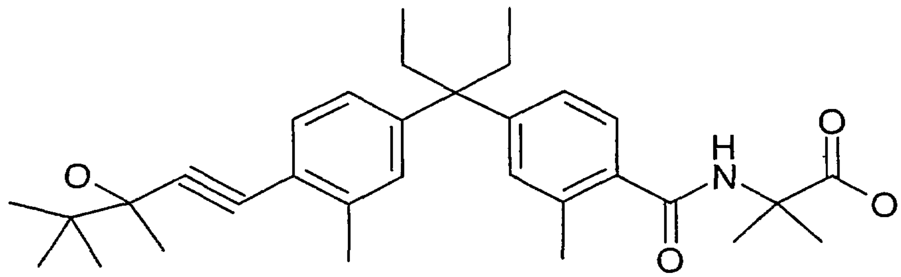
and



Additional particularly preferred are compounds or a pharmaceutically acceptable salt or prodrug derivative thereof selected from (TBU-1) to (TBU-86), as follows:

A compound or a pharmaceutically acceptable salt oran ester prodrug derivative thereof selected from (TBU-1) to (TBU-86), as follows:

TBU-1)



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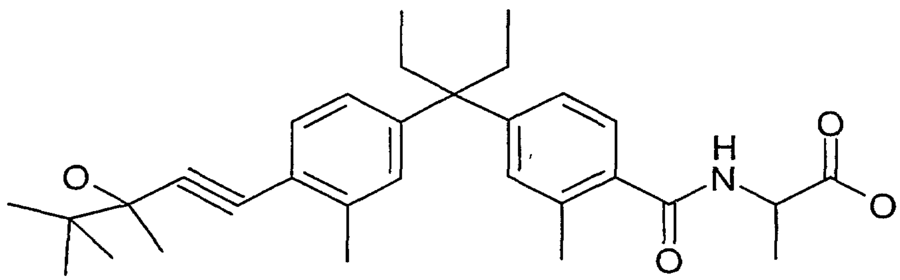
TBU-2)



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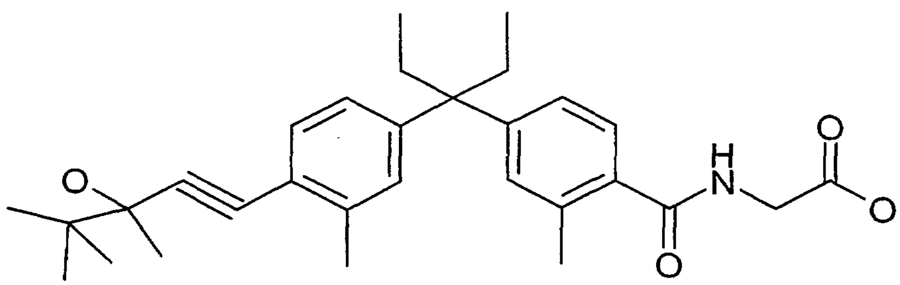
TBU-3)



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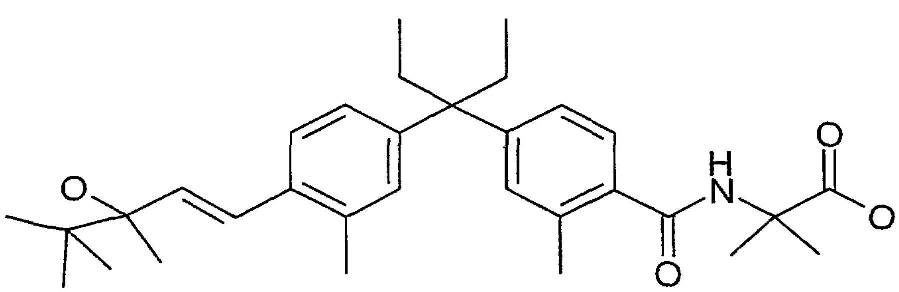
TBU-4)



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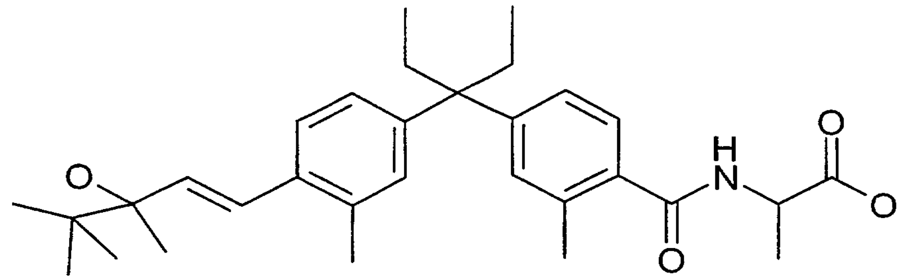
TBU-5)



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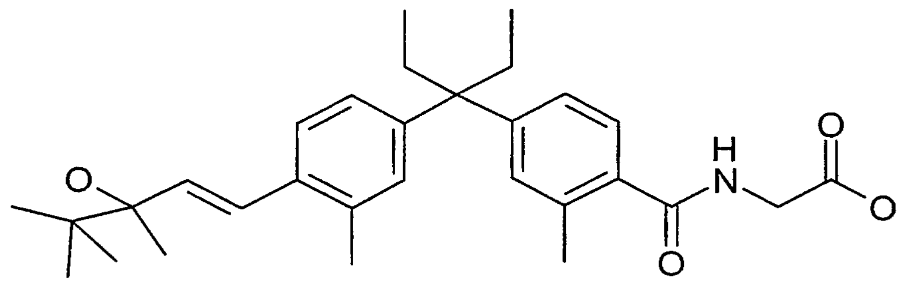
TBU-6)



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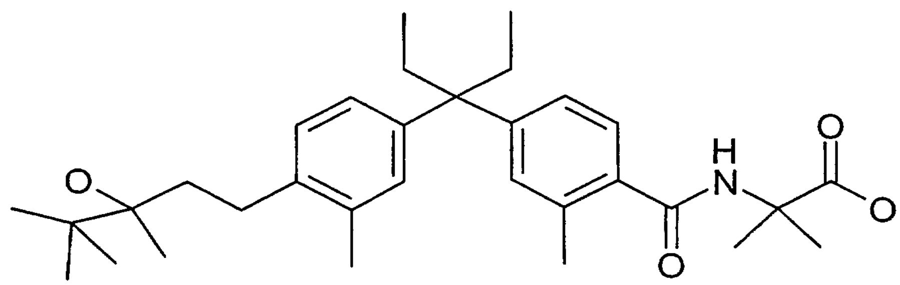
TBU-7)



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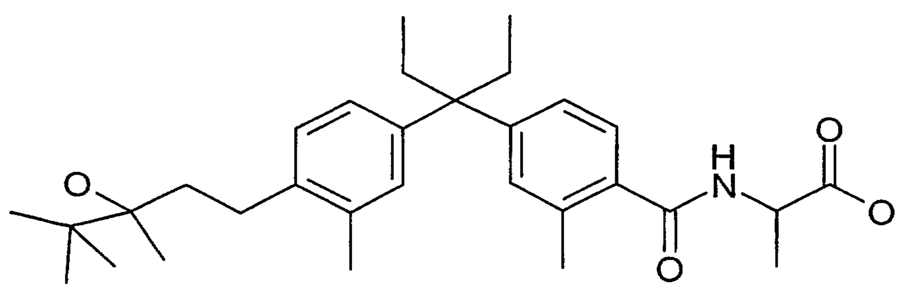
TBU-8)



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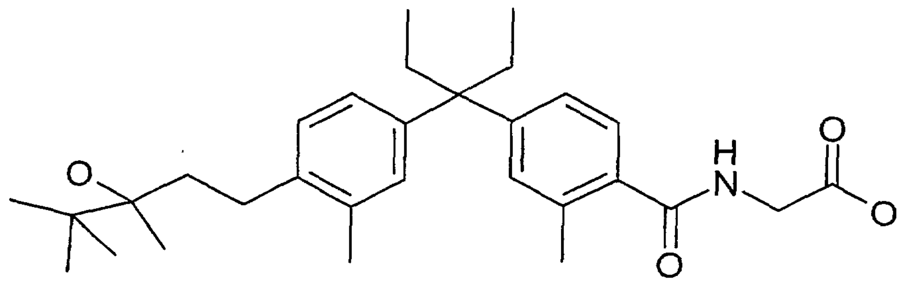
TBU-9)



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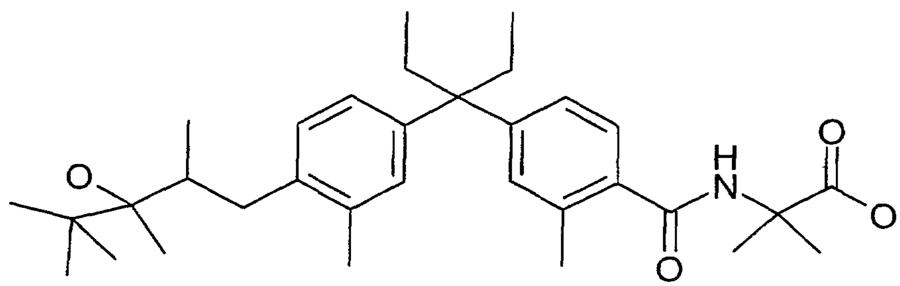

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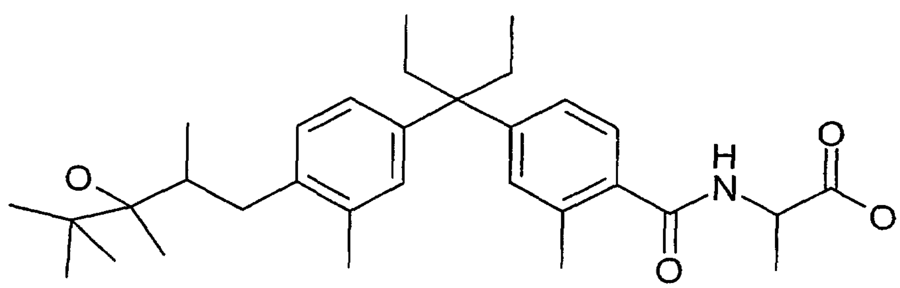

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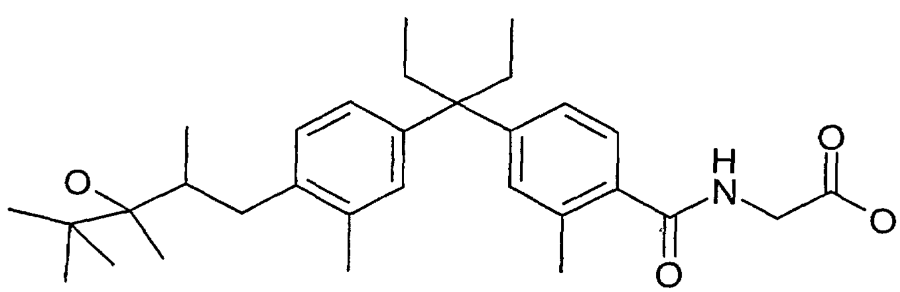

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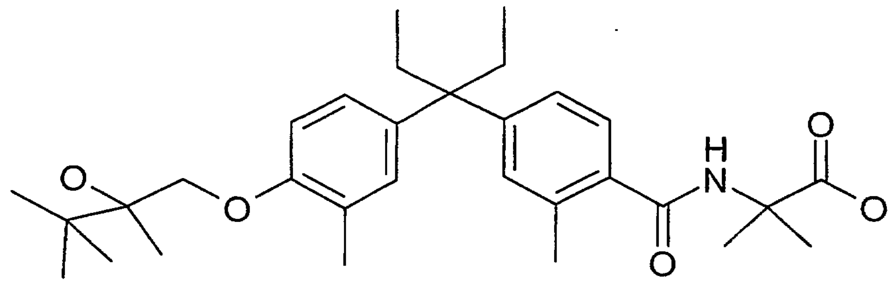

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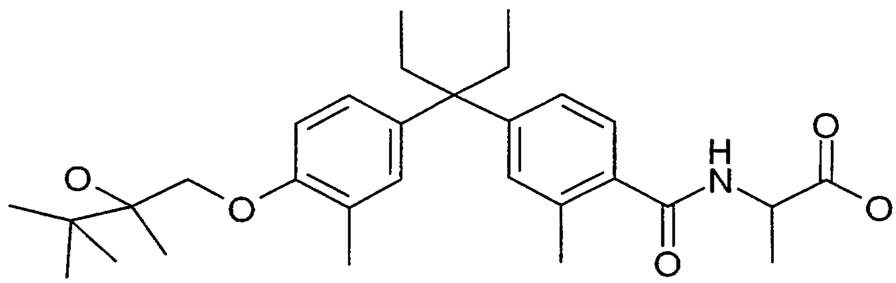

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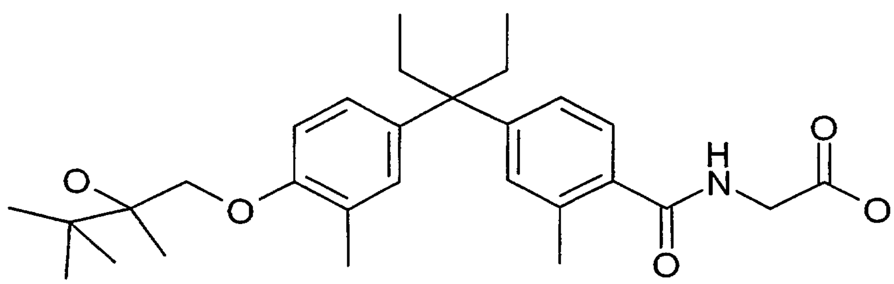
TBU-15)



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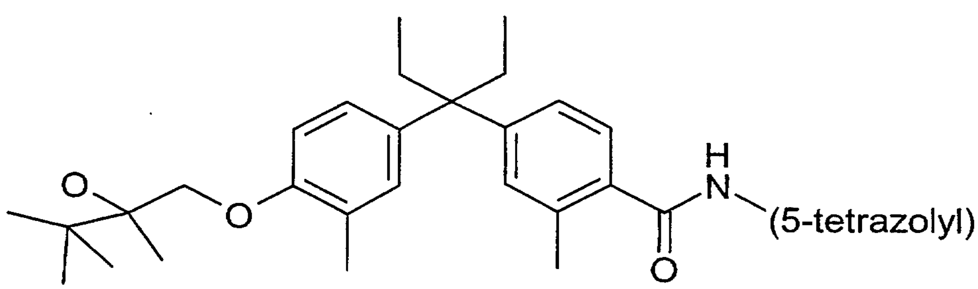
TBU-16)



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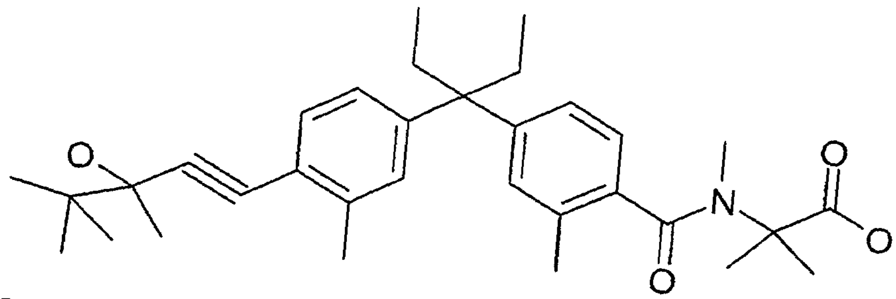

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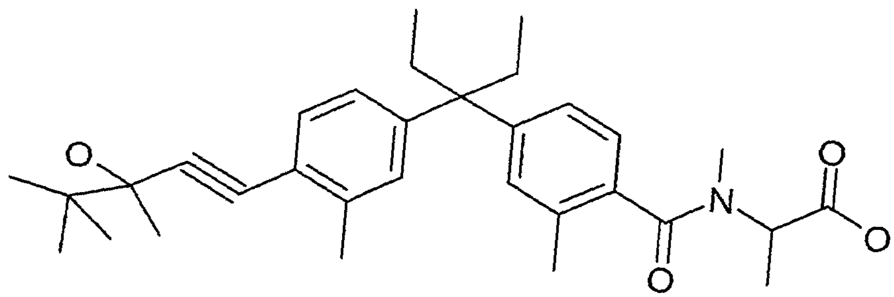

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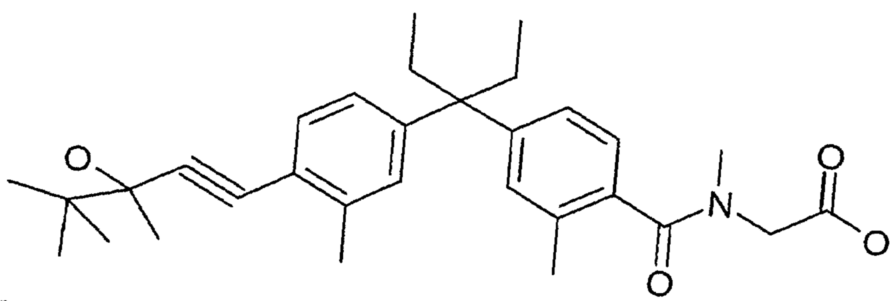

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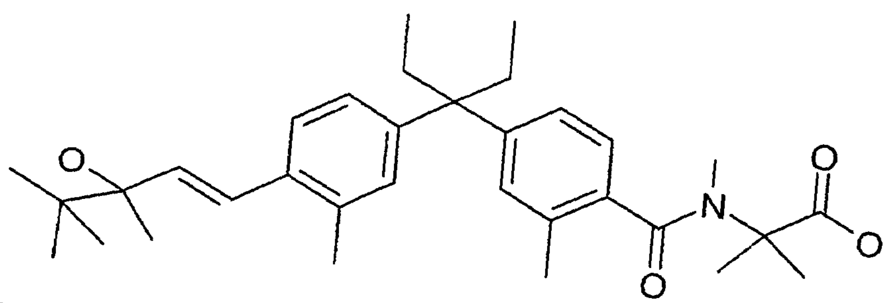

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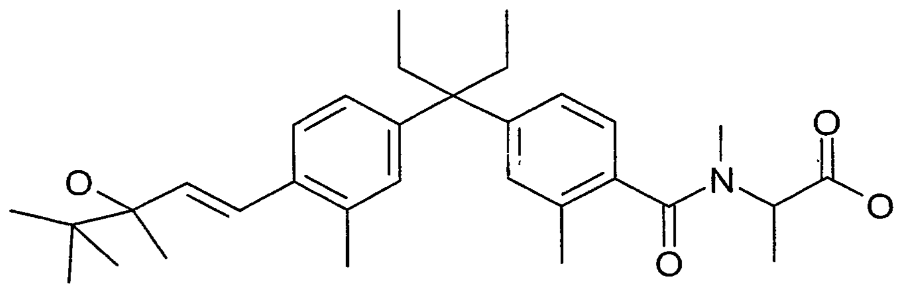

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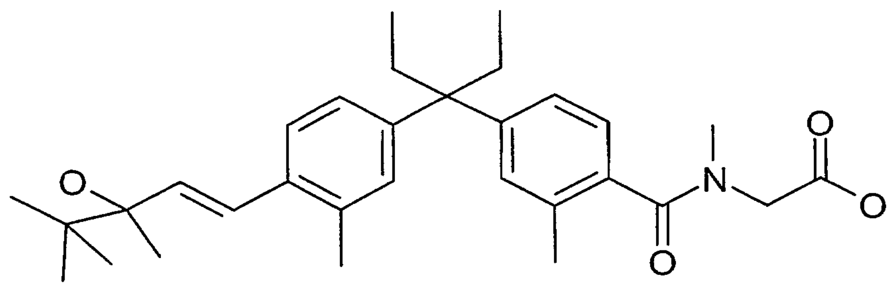

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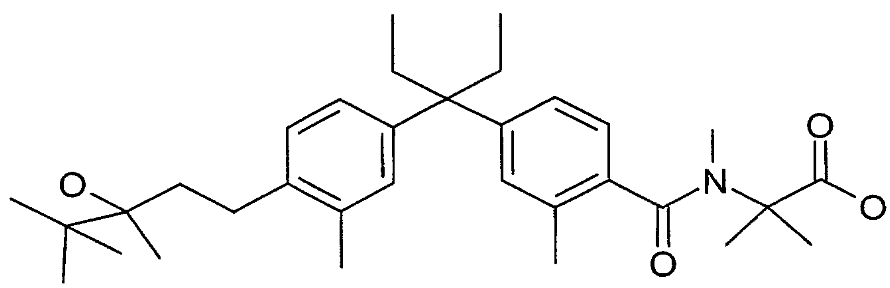

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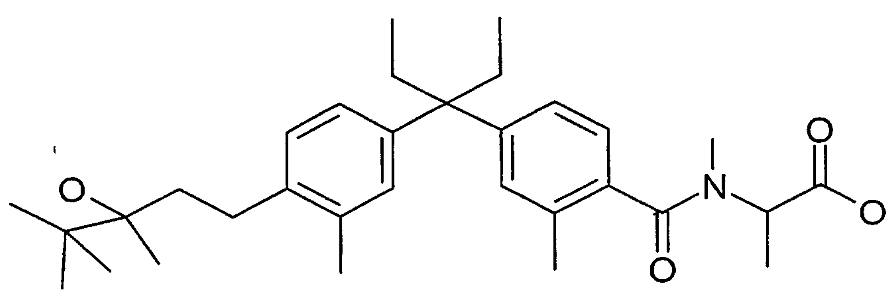

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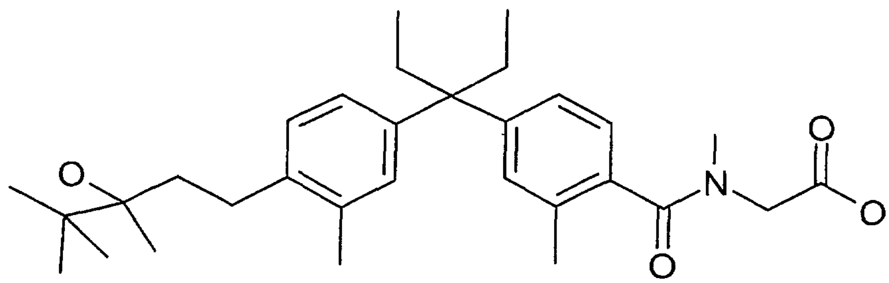

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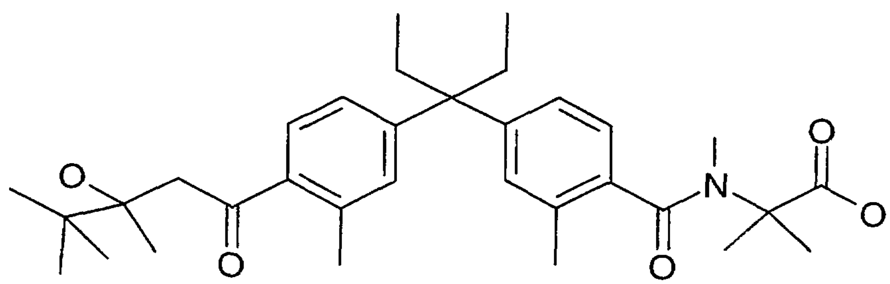

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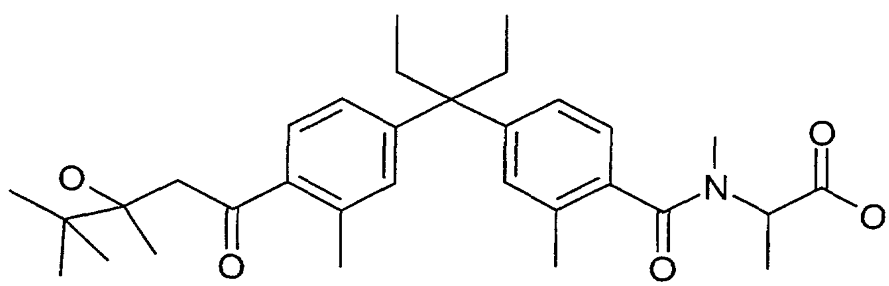

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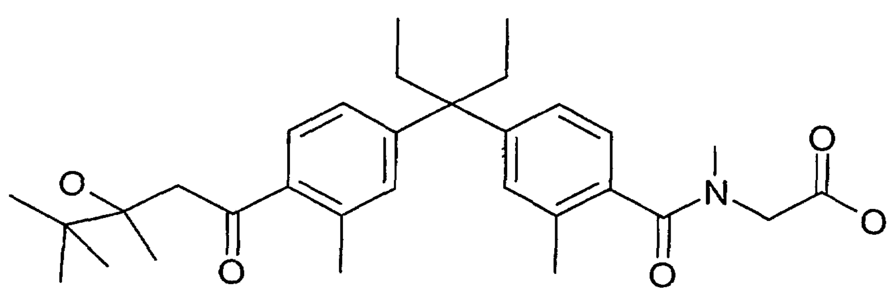

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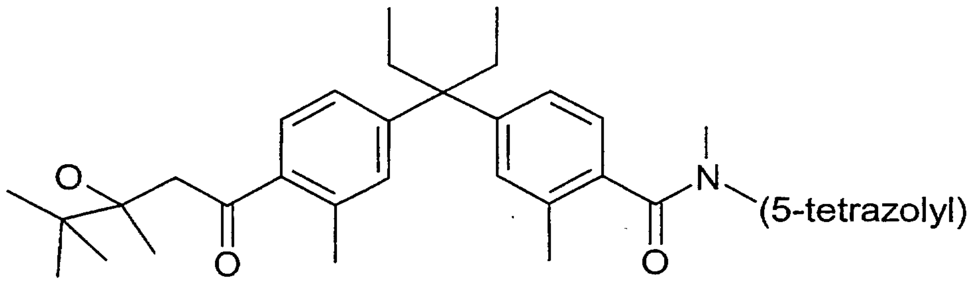

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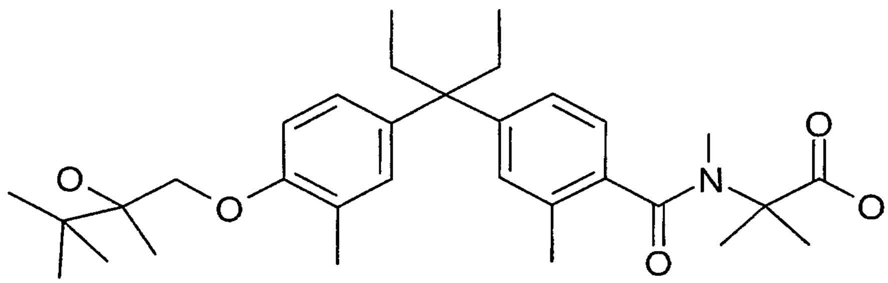

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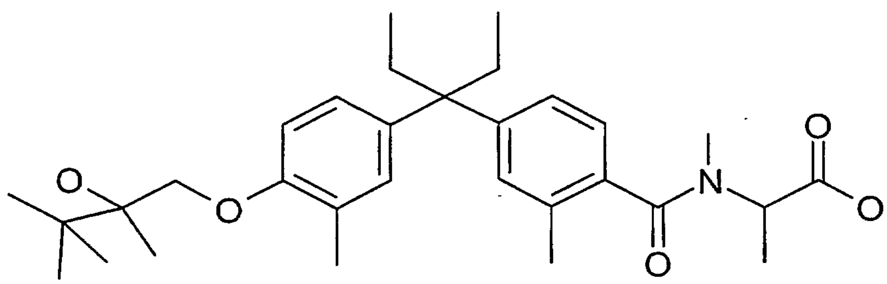

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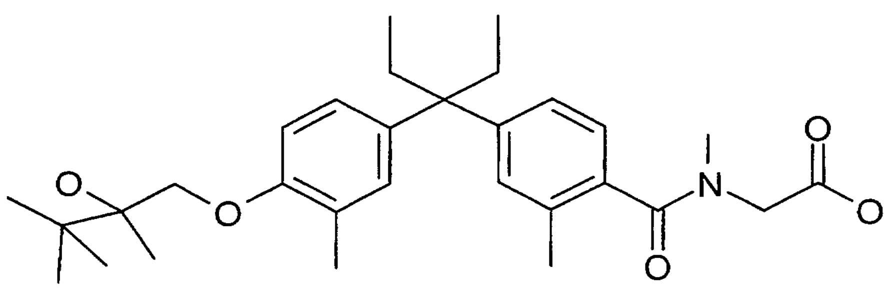

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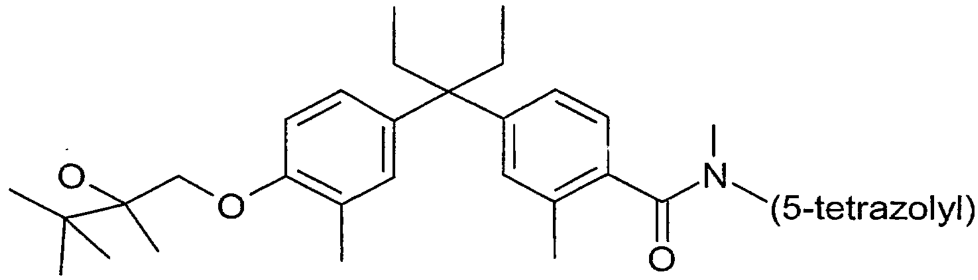

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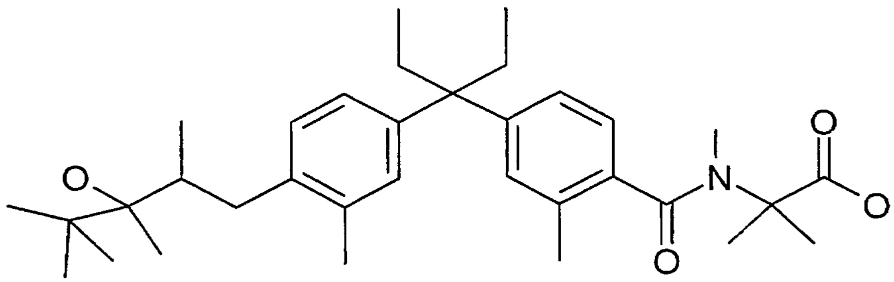

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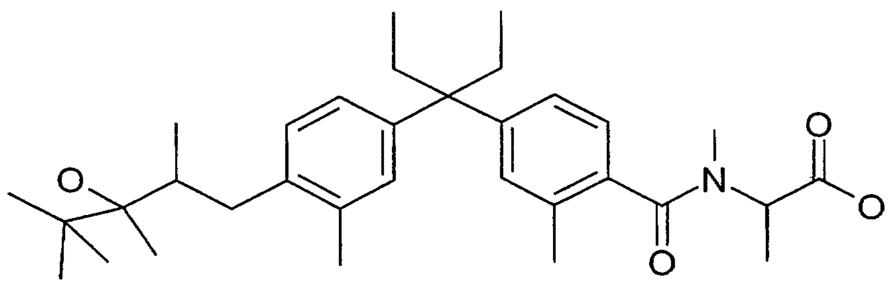

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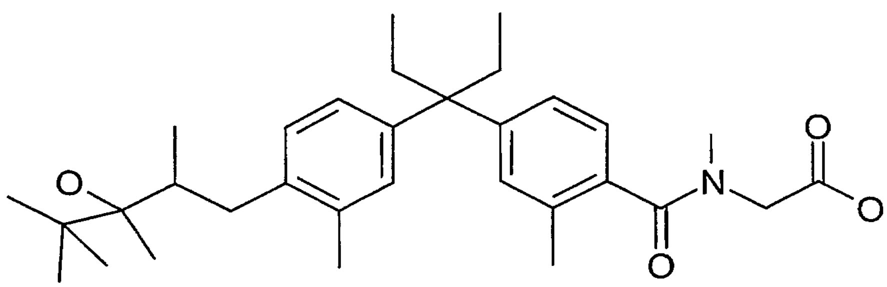

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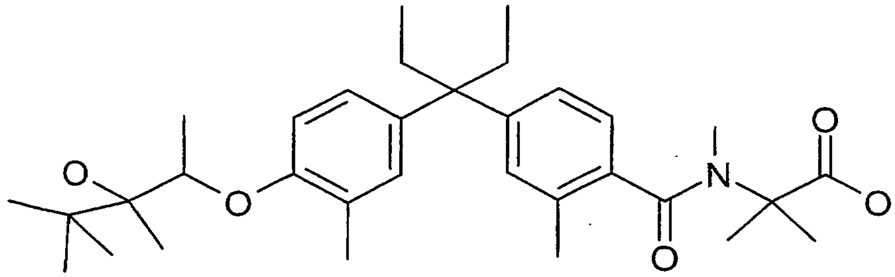

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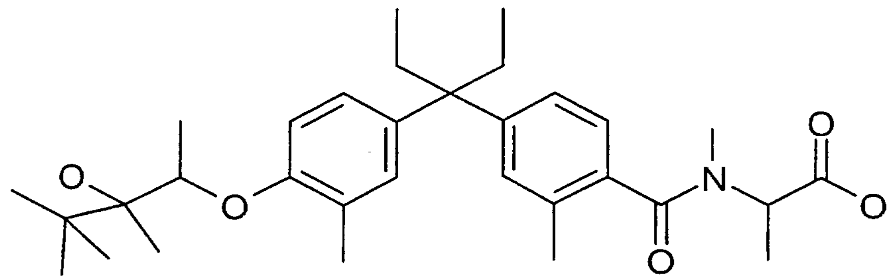

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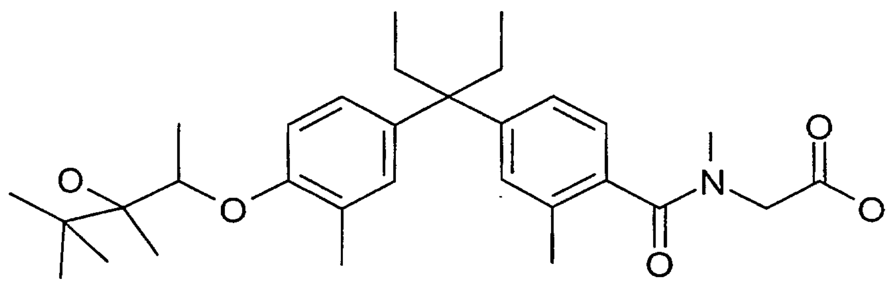

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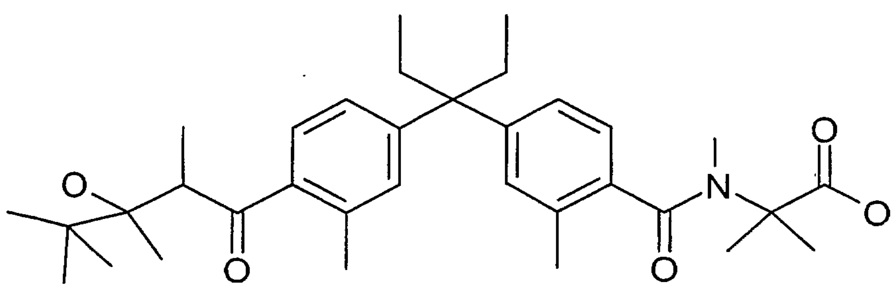

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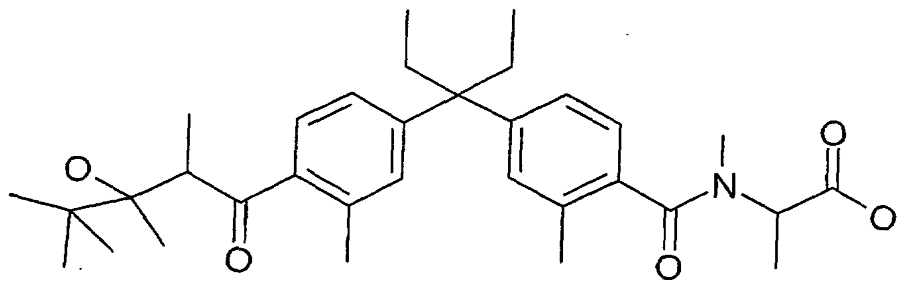

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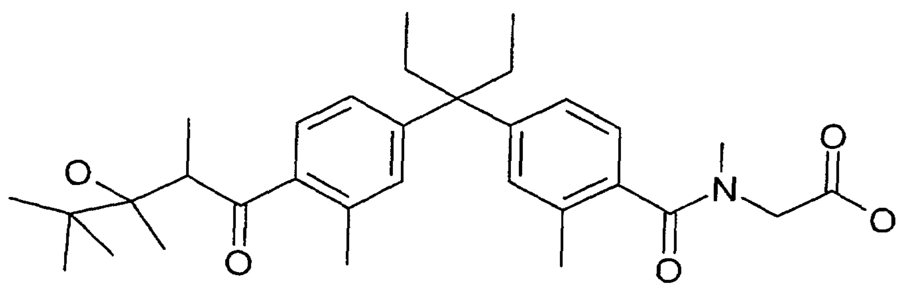

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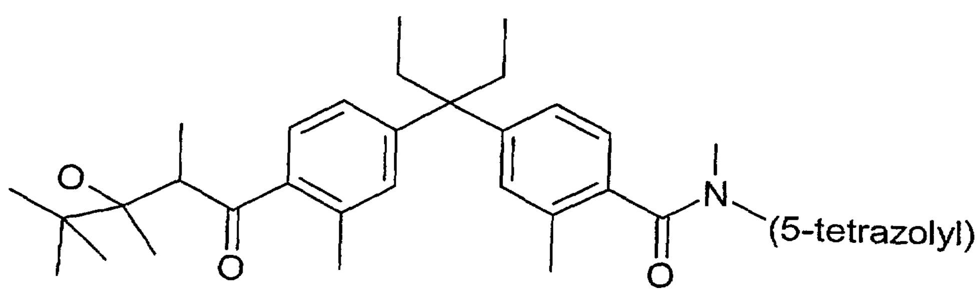

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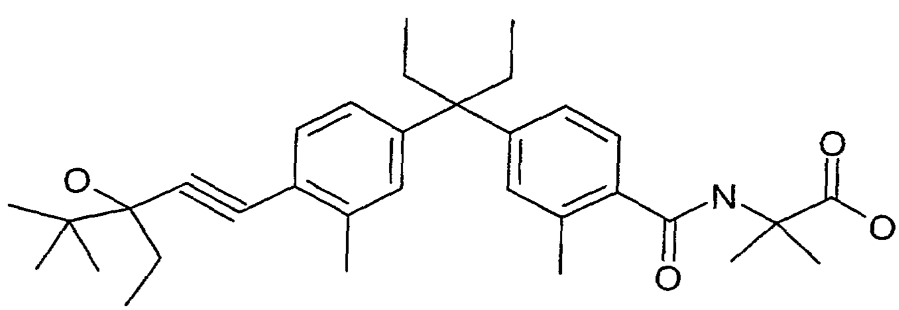

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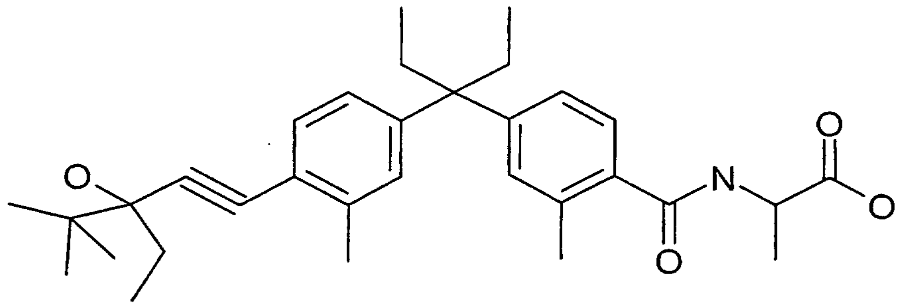

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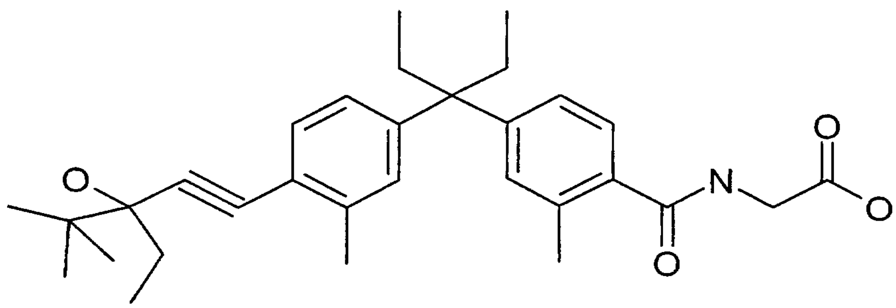

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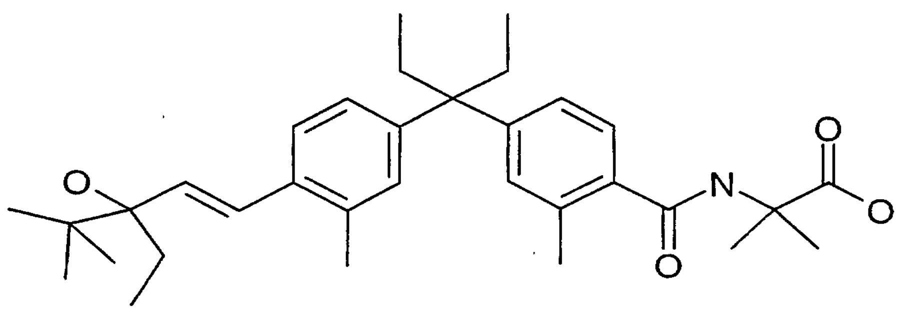

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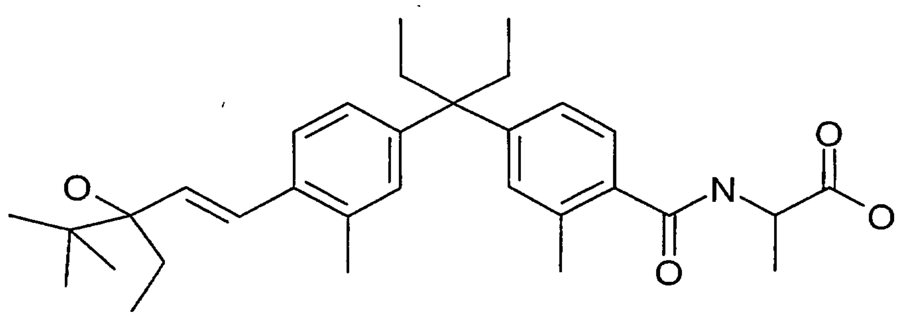

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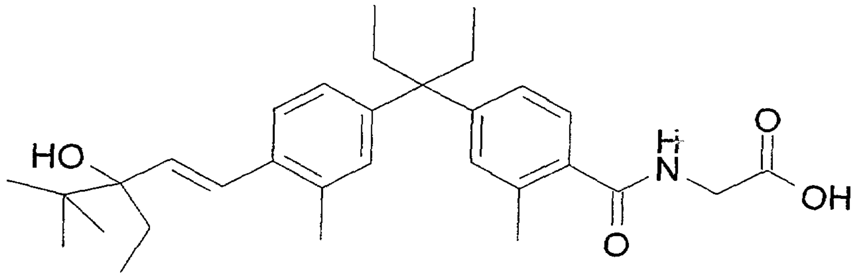

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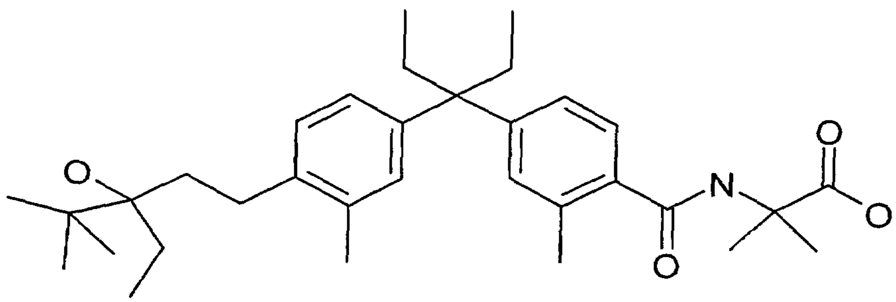

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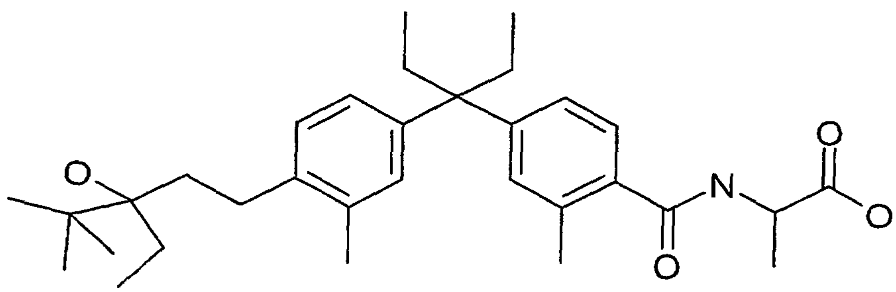

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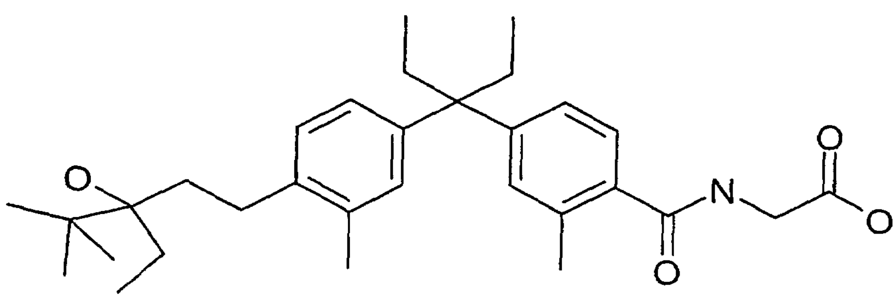

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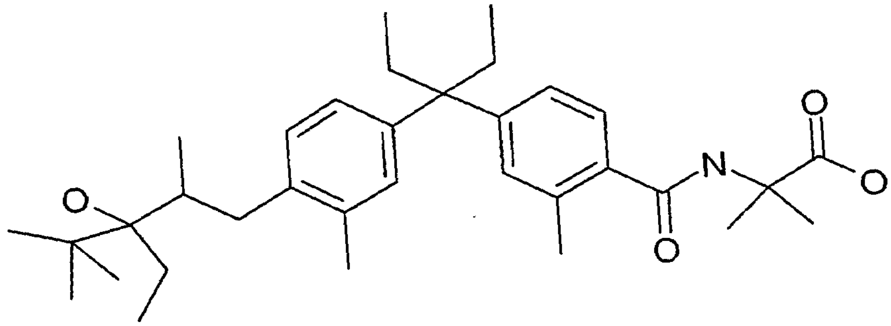

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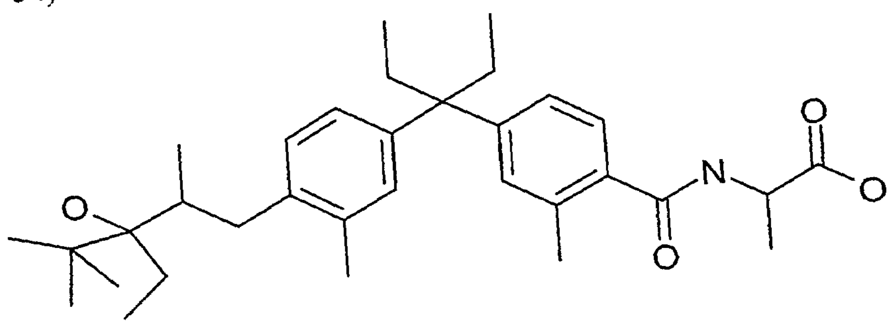

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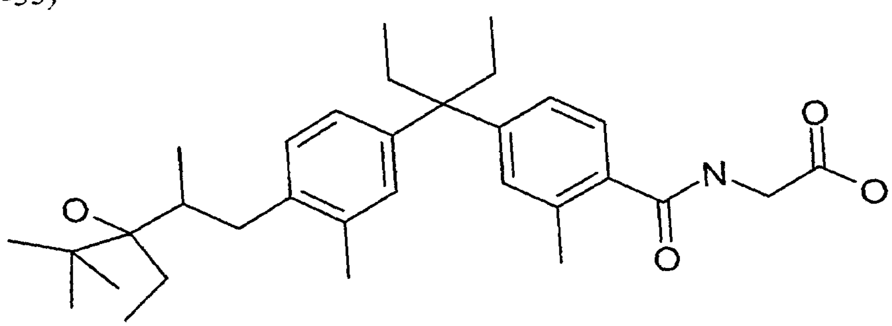

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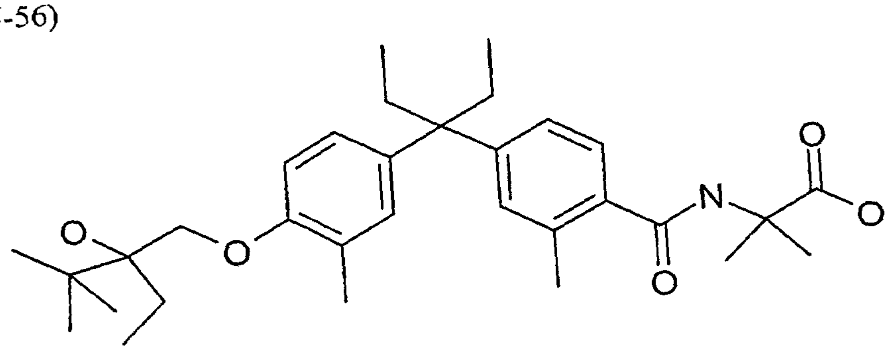

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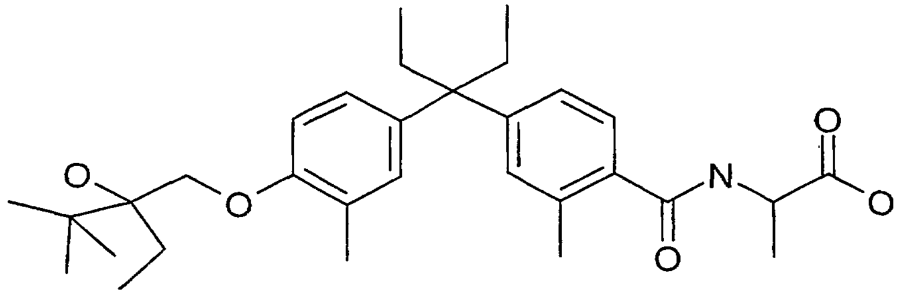

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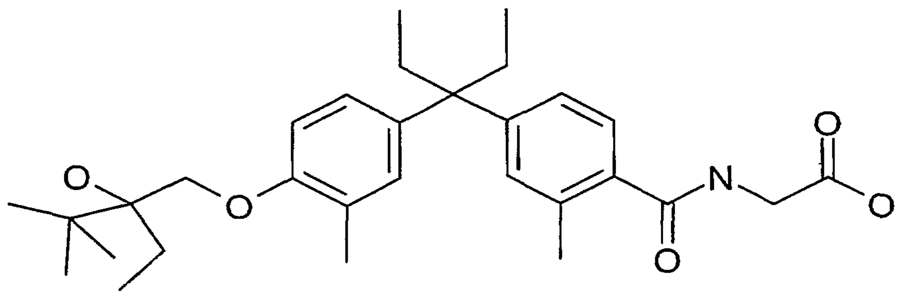

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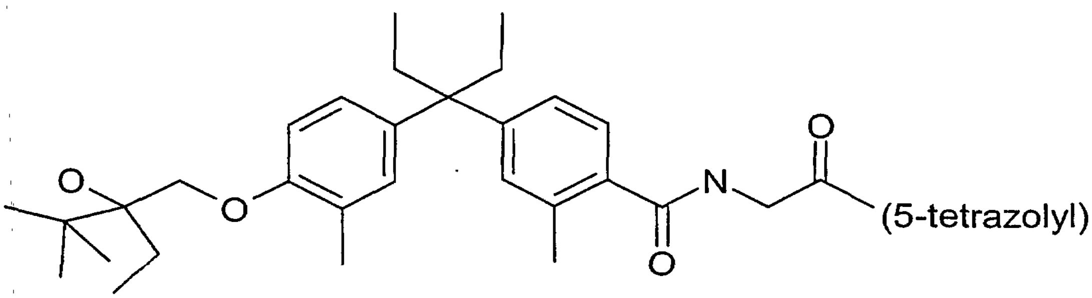

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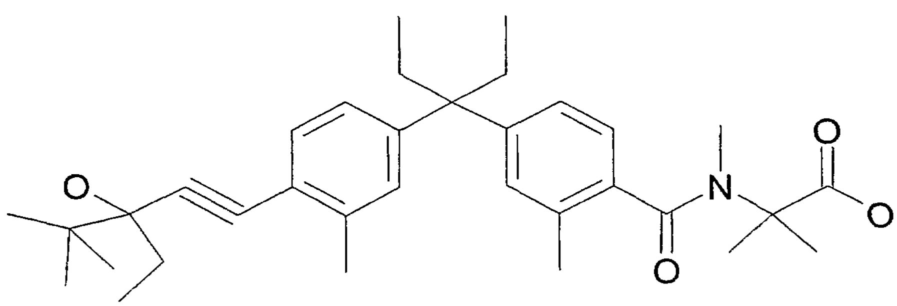

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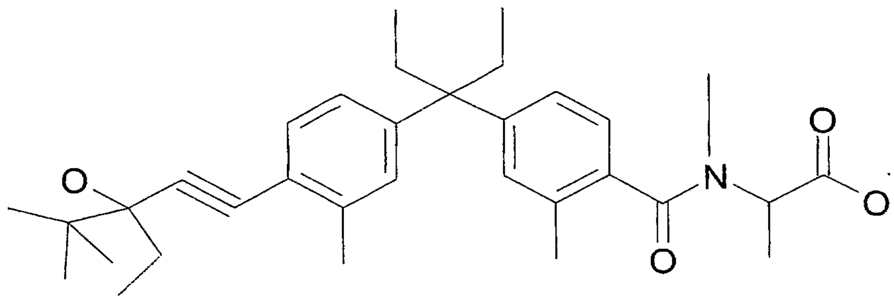

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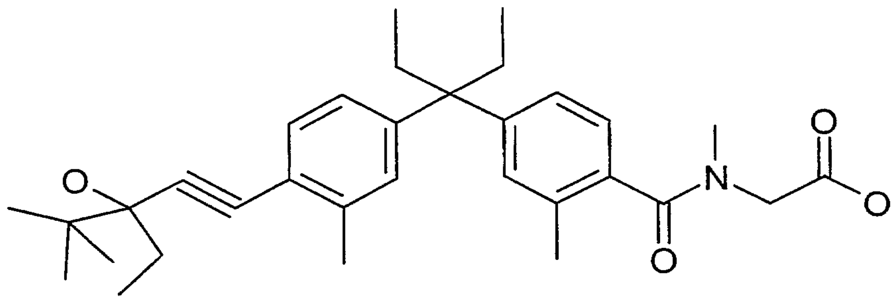

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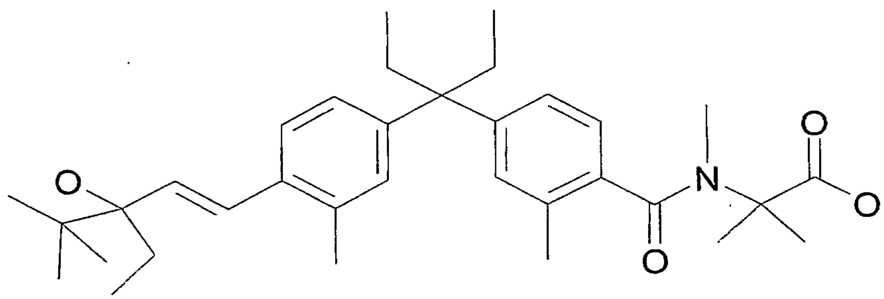

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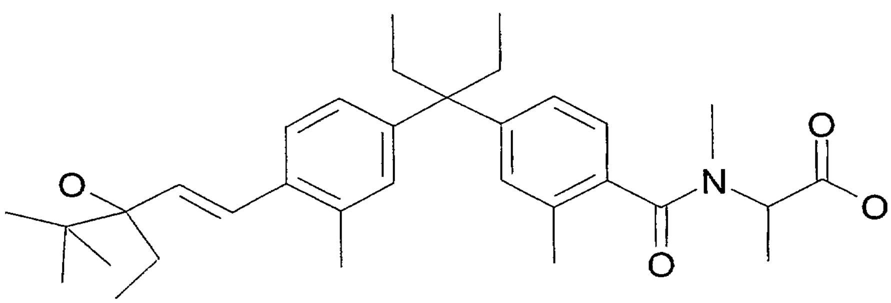

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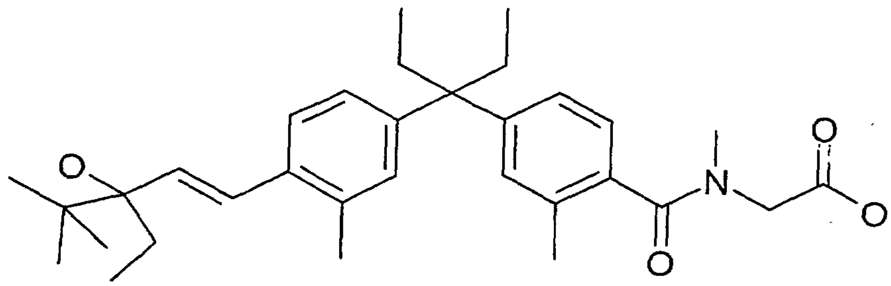

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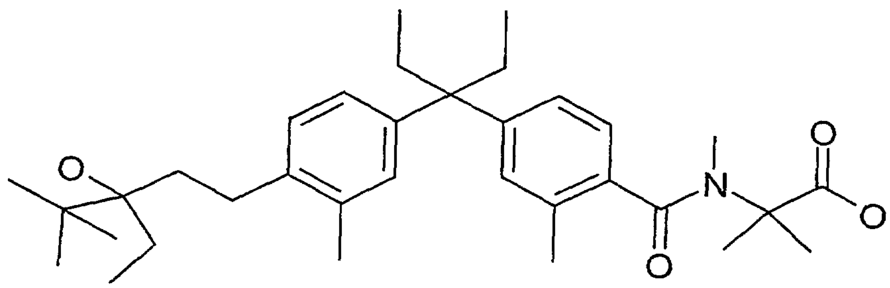

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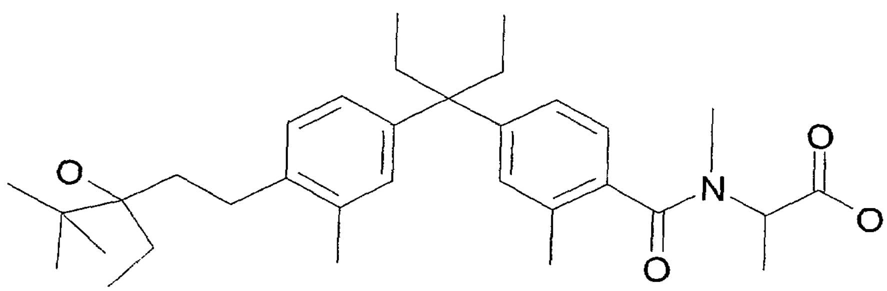

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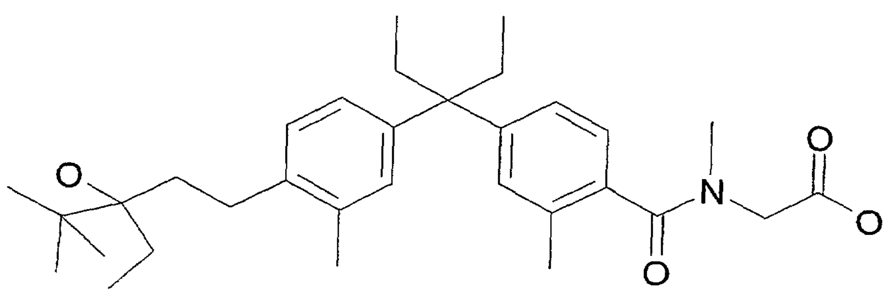

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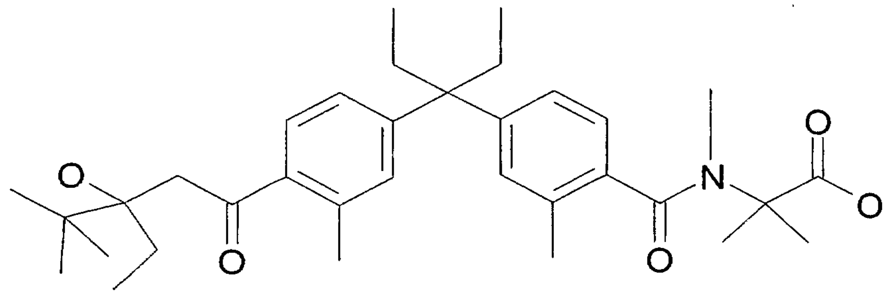

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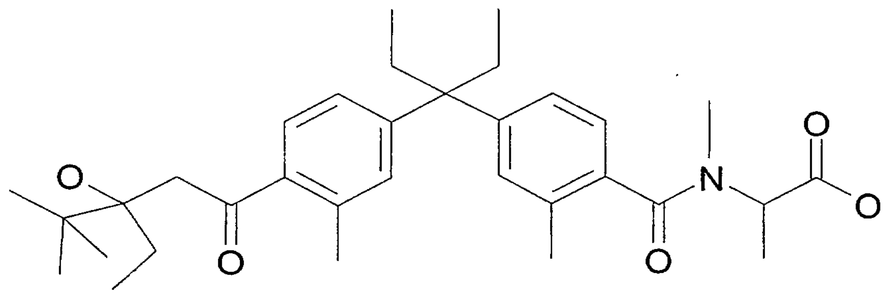

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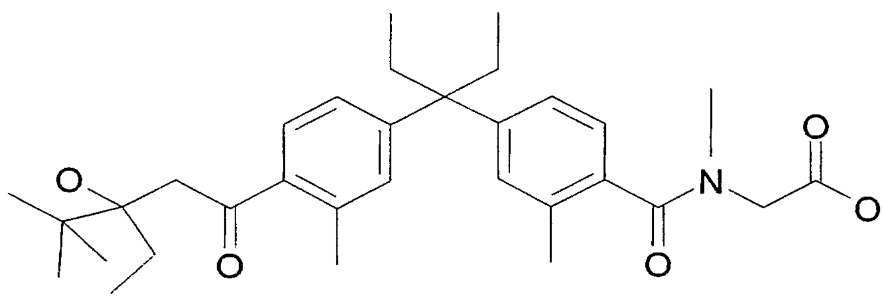

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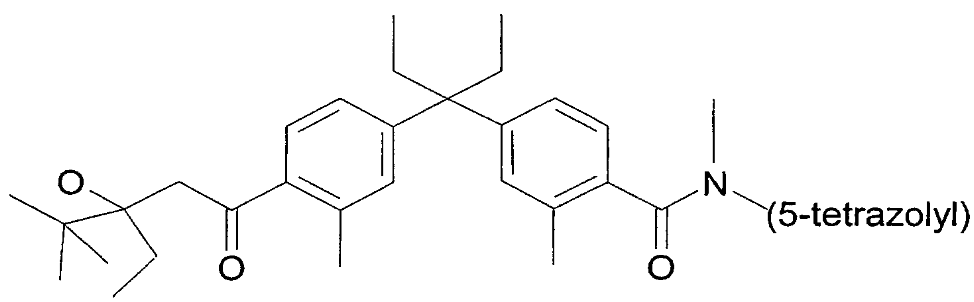

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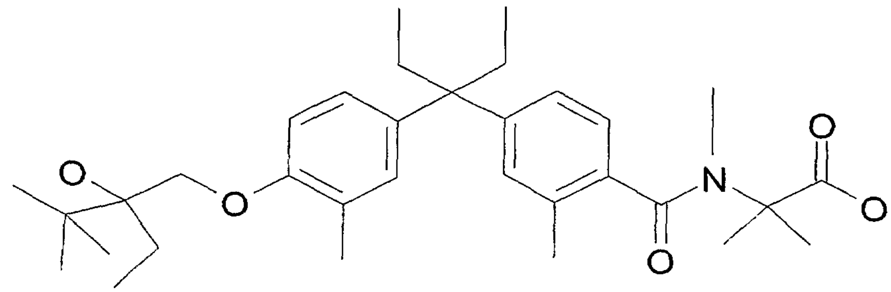

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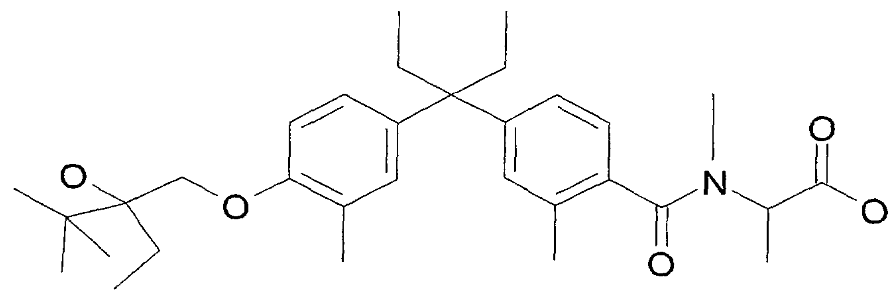

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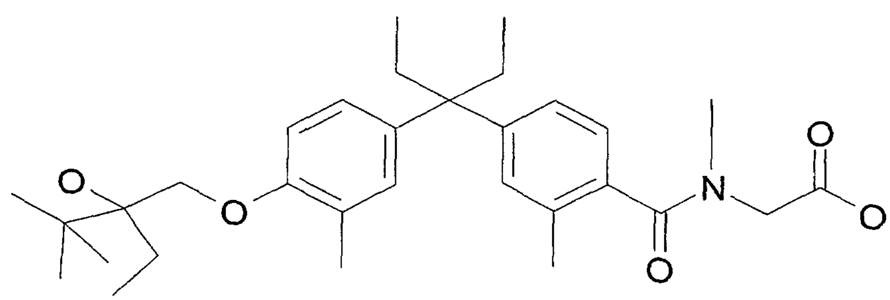

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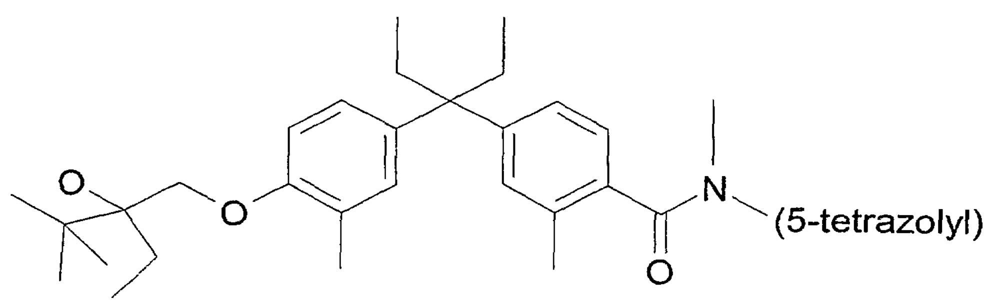

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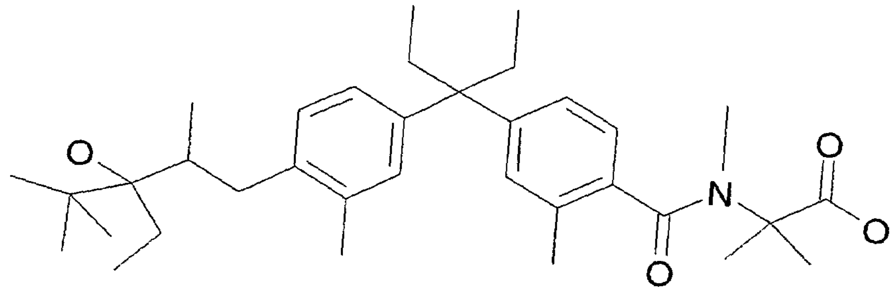

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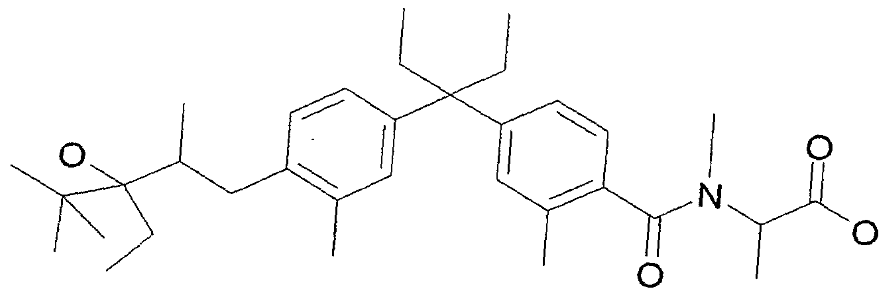

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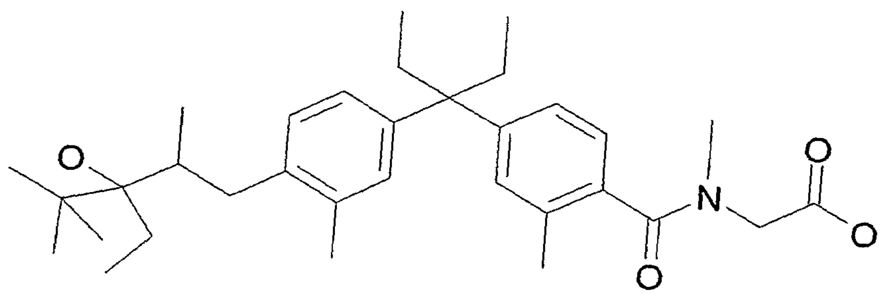

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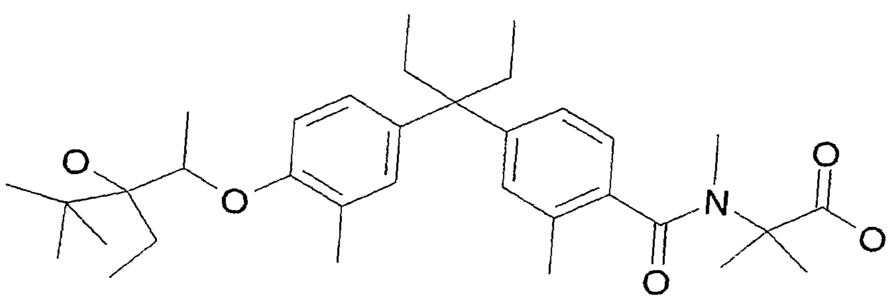

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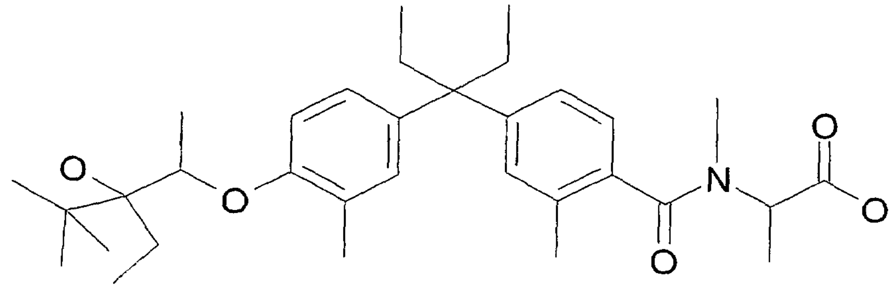

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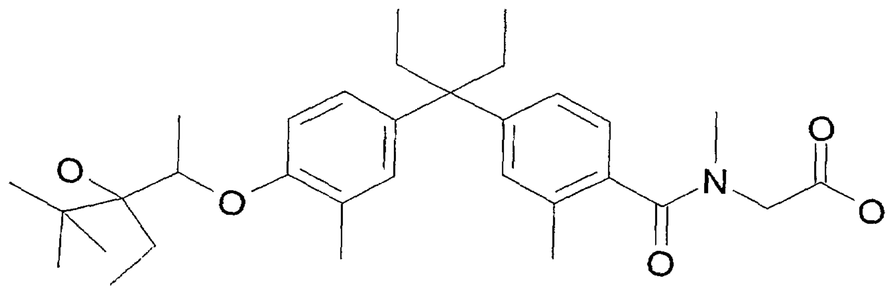

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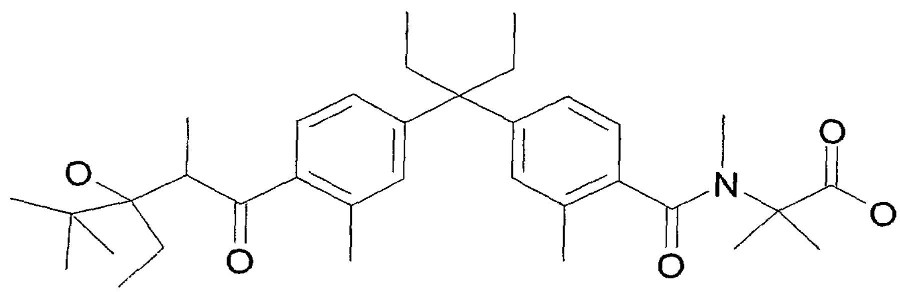

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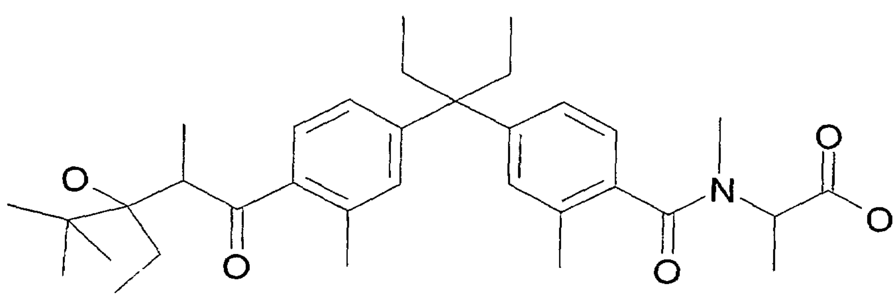

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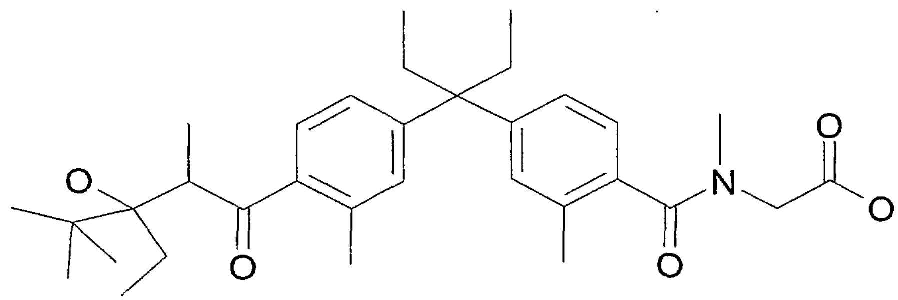

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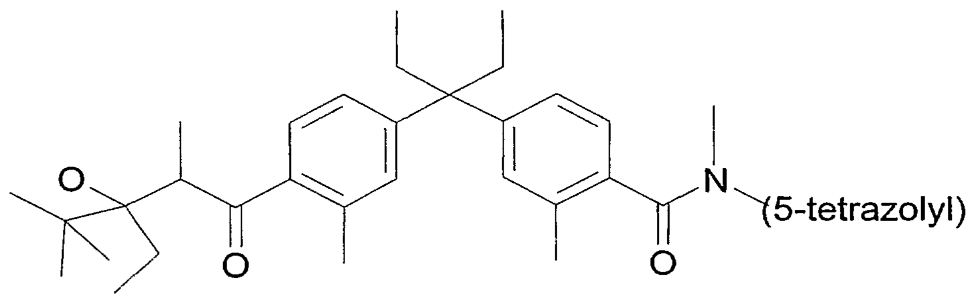
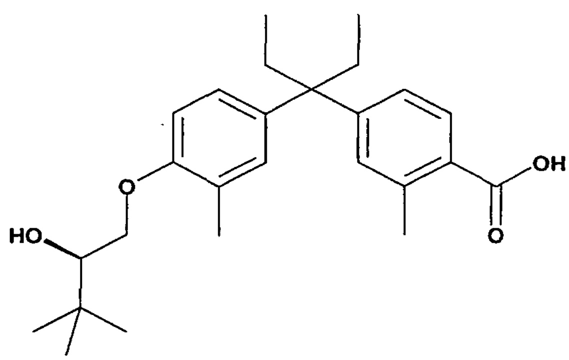
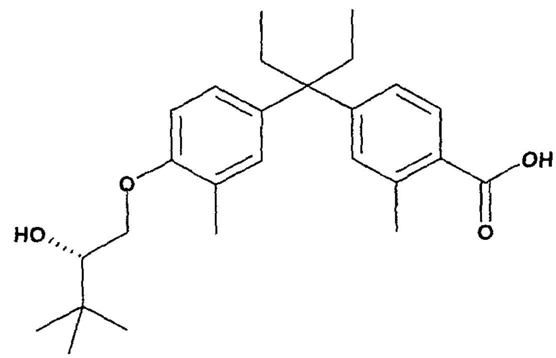
TBU-86)



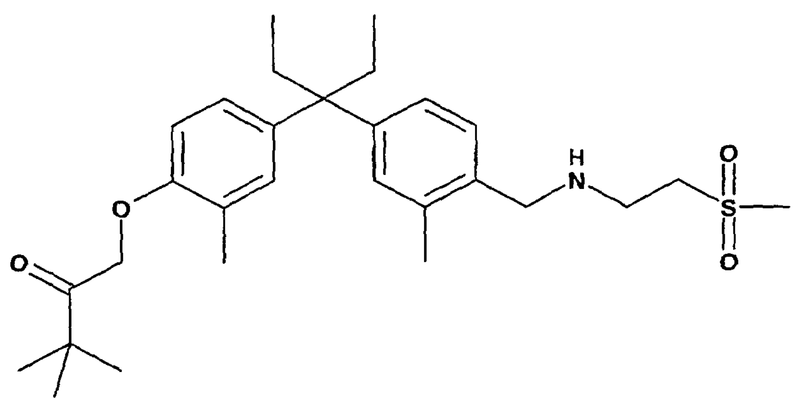
Particularly preferred as a compound of the invention is the compound or a pharmaceutically acceptable salt or ester prodrug derivative of the compound represented by the formula:



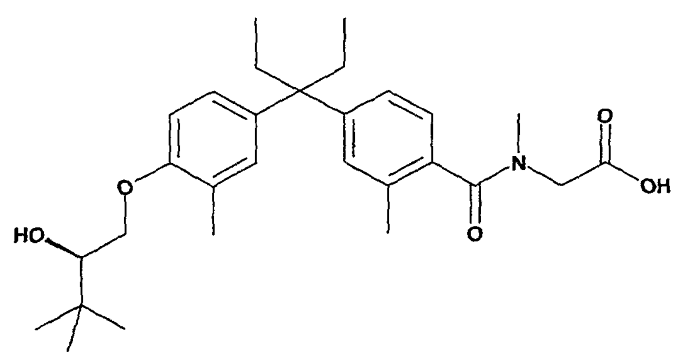
or



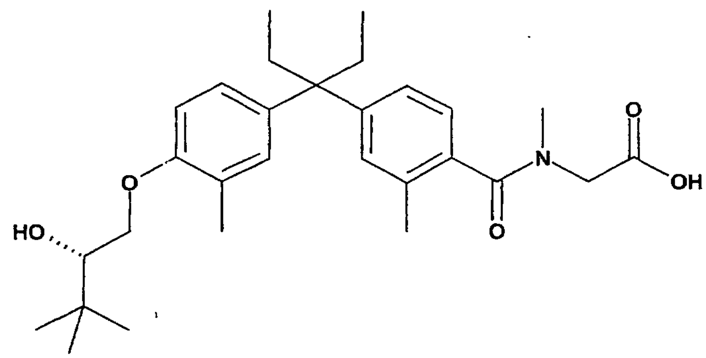
or



Particularly preferred as a compound of the invention is the compound or a pharmaceutically acceptable salt or ester prodrug derivative of the compound represented by the formula:



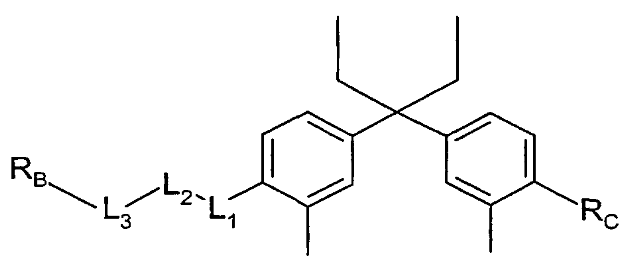
or



For all of the above compounds of the invention defined by Formula (I) the preferred prodrug derivative is a methyl ester, ethyl ester N,N-diethylglycolamido ester or morpholinylethyl ester. In addition, for all of the above compounds of the invention the preferred salt is sodium or potassium.

Other specific compounds that are preferred embodiments of this invention and are preferred for for practicing the method of treatment of the invention are set out in the following Tables. All numbers in the Tables cells reciting chemical species are to be understood as subscripts in chemical formulae, for example, in the first row of Table 1, Compound No. 1, the symbol, "CO2Me" is to be understood as the conventional chemical nomenclature, -- CO_2H --. Each row of the Tables 1 and 2 represents a single compound having an identifying defining the specific substituents in the structural formula displayed above each Tables, as follows:

Among other preferred compounds of the invention are those represented by the formula:



and pharmaceutically acceptable salts thereof; wherein;

said compound is selected from a compound code numbered 1 thru 468, with each

compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the row following the compound code number, as set out in the following Table 1 :

Table 1

No.	R_B	L_3	L_2	L_1	R_C
1	tBu	C(O)	CH2	O	C(O)CH(Me)CH2CO2H
2	tBu	CHOH	CH2	O	C(O)CH(Me)CH2CO2H
3	tBu	C(Me)OH	CH2	O	C(O)CH(Me)CH2CO2H
4	tBu	C(O)	CH(Me)	O	C(O)CH(Me)CH2CO2H
5	tBu	CHOH	CH(Me)	O	C(O)CH(Me)CH2CO2H
6	tBu	C(Me)OH	CH(Me)	O	C(O)CH(Me)CH2CO2H
7	tBu	C(O)	CH2	O	CO2H
8	tBu	CHOH	CH2	O	CO2H
9	tBu	C(Me)OH	CH2	O	CO2H
10	tBu	C(O)	CH(Me)	O	CO2H
11	tBu	CHOH	CH(Me)	O	CO2H
12	tBu	C(Me)OH	CH(Me)	O	CO2H
13	tBu	C(O)	CH2	O	C(O)NH2
14	tBu	CHOH	CH2	O	C(O)NH2
15	tBu	C(Me)OH	CH2	O	C(O)NH2
16	tBu	C(O)	CH(Me)	O	C(O)NH2
17	tBu	CHOH	CH(Me)	O	C(O)NH2
18	tBu	C(Me)OH	CH(Me)	O	C(O)NH2
19	tBu	C(O)	CH2	O	C(O)NMe2
20	tBu	CHOH	CH2	O	C(O)NMe2
21	tBu	C(Me)OH	CH2	O	C(O)NMe2
22	tBu	C(O)	CH(Me)	O	C(O)NMe2
23	tBu	CHOH	CH(Me)	O	C(O)NMe2
24	tBu	C(Me)OH	CH(Me)	O	C(O)NMe2
25	tBu	C(O)	CH2	O	5-tetrazolyl
26	tBu	CHOH	CH2	O	5-tetrazolyl
27	tBu	C(Me)OH	CH2	O	5-tetrazolyl

28	tBu	C(O)	CH(Me)	O	5-tetrazolyl
29	tBu	CHOH	CH(Me)	O	5-tetrazolyl
30	tBu	C(Me)OH	CH(Me)	O	5-tetrazolyl
31	tBu	C(O)	CH2	O	C(O)-NH-5-tetrazolyl
32	tBu	CHOH	CH2	O	C(O)-NH-5-tetrazolyl
33	tBu	C(Me)OH	CH2	O	C(O)-NH-5-tetrazolyl
34	tBu	C(O)	CH(Me)	O	C(O)-NH-5-tetrazolyl
35	tBu	CHOH	CH(Me)	O	C(O)-NH-5-tetrazolyl
36	tBu	C(Me)OH	CH(Me)	O	C(O)-NH-5-tetrazolyl
37	tBu	C(O)	CH2	O	C(O)NHCH2SO2Me
38	tBu	CHOH	CH2	O	C(O)NHCH2SO2Me
39	tBu	C(Me)OH	CH2	O	C(O)NHCH2SO2Me
40	tBu	C(O)	CH(Me)	O	C(O)NHCH2SO2Me
41	tBu	CHOH	CH(Me)	O	C(O)NHCH2SO2Me
42	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2SO2Me
43	tBu	C(O)	CH2	O	C(O)NHCH2S(O)Me
44	tBu	CHOH	CH2	O	C(O)NHCH2S(O)Me
45	tBu	C(Me)OH	CH2	O	C(O)NHCH2S(O)Me
46	tBu	C(O)	CH(Me)	O	C(O)NHCH2S(O)Me
47	tBu	CHOH	CH(Me)	O	C(O)NHCH2S(O)Me
48	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2S(O)Me
49	tBu	C(O)	CH2	O	C(O)NHCH2CH2SO2Me
50	tBu	CHOH	CH2	O	C(O)NHCH2CH2SO2Me
51	tBu	C(Me)OH	CH2	O	C(O)NHCH2CH2SO2Me
52	tBu	C(O)	CH(Me)	O	C(O)NHCH2CH2SO2Me
53	tBu	CHOH	CH(Me)	O	C(O)NHCH2CH2SO2Me
54	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2CH2SO2Me
55	tBu	C(O)	CH2	O	C(O)NHCH2CH2S(O)Me
56	tBu	CHOH	CH2	O	C(O)NHCH2CH2S(O)Me
57	tBu	C(Me)OH	CH2	O	C(O)NHCH2CH2S(O)Me
58	tBu	C(O)	CH(Me)	O	C(O)NHCH2CH2S(O)Me

59	tBu	CHOH	CH(Me)	O	C(O)NHCH2CH2S(O)Me
60	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2CH2S(O)Me
61	tBu	C(O)	CH2	O	C(O)NHSO2Me
62	tBu	CHOH	CH2	O	C(O)NHSO2Me
63	tBu	C(Me)OH	CH2	O	C(O)NHSO2Me
64	tBu	C(O)	CH(Me)	O	C(O)NHSO2Me
65	tBu	CHOH	CH(Me)	O	C(O)NHSO2Me
66	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2Me
67	tBu	C(O)	CH2	O	C(O)NHS(O)Me
68	tBu	CHOH	CH2	O	C(O)NHS(O)Me
69	tBu	C(Me)OH	CH2	O	C(O)NHS(O)Me
70	tBu	C(O)	CH(Me)	O	C(O)NHS(O)Me
71	tBu	CHOH	CH(Me)	O	C(O)NHS(O)Me
72	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)Me
73	tBu	C(O)	CH2	O	C(O)NHSO2Et
74	tBu	CHOH	CH2	O	C(O)NHSO2Et
75	tBu	C(Me)OH	CH2	O	C(O)NHSO2Et
76	tBu	C(O)	CH(Me)	O	C(O)NHSO2Et
77	tBu	CHOH	CH(Me)	O	C(O)NHSO2Et
78	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2Et
79	tBu	C(O)	CH2	O	C(O)NHS(O)Et
80	tBu	CHOH	CH2	O	C(O)NHS(O)Et
81	tBu	C(Me)OH	CH2	O	C(O)NHS(O)Et
82	tBu	C(O)	CH(Me)	O	C(O)NHS(O)Et
83	tBu	CHOH	CH(Me)	O	C(O)NHS(O)Et
84	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)Et
85	tBu	C(O)	CH2	O	C(O)NHSO2iPr
86	tBu	CHOH	CH2	O	C(O)NHSO2iPr
87	tBu	C(Me)OH	CH2	O	C(O)NHSO2iPr
88	tBu	C(O)	CH(Me)	O	C(O)NHSO2iPr
89	tBu	CHOH	CH(Me)	O	C(O)NHSO2iPr

90	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2iPr
91	tBu	C(O)	CH2	O	C(O)NHS(O)iPr
92	tBu	CHOH	CH2	O	C(O)NHS(O)iPr
93	tBu	C(Me)OH	CH2	O	C(O)NHS(O)iPr
94	tBu	C(O)	CH(Me)	O	C(O)NHS(O)iPr
95	tBu	CHOH	CH(Me)	O	C(O)NHS(O)iPr
96	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)iPr
97	tBu	C(O)	CH2	O	C(O)NHSO2tBu
98	tBu	CHOH	CH2	O	C(O)NHSO2tBu
99	tBu	C(Me)OH	CH2	O	C(O)NHSO2tBu
100	tBu	C(O)	CH(Me)	O	C(O)NHSO2tBu
101	tBu	CHOH	CH(Me)	O	C(O)NHSO2tBu
102	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2tBu
103	tBu	C(O)	CH2	O	C(O)NHS(O)tBu
104	tBu	CHOH	CH2	O	C(O)NHS(O)tBu
105	tBu	C(Me)OH	CH2	O	C(O)NHS(O)tBu
106	tBu	C(O)	CH(Me)	O	C(O)NHS(O)tBu
107	tBu	CHOH	CH(Me)	O	C(O)NHS(O)tBu
108	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)tBu
109	tBu	C(O)	CH2	O	CH2NHSO2Me
110	tBu	CHOH	CH2	O	CH2NHSO2Me
111	tBu	C(Me)OH	CH2	O	CH2NHSO2Me
112	tBu	C(O)	CH(Me)	O	CH2NHSO2Me
113	tBu	CHOH	CH(Me)	O	CH2NHSO2Me
114	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2Me
115	tBu	C(O)	CH2	O	CH2NHS(O)Me
116	tBu	CHOH	CH2	O	CH2NHS(O)Me
117	tBu	C(Me)OH	CH2	O	CH2NHS(O)Me
118	tBu	C(O)	CH(Me)	O	CH2NHS(O)Me
119	tBu	CHOH	CH(Me)	O	CH2NHS(O)Me
120	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)Me

121	tBu	C(O)	CH2	O	CH2NHSO2Et
122	tBu	CHOH	CH2	O	CH2NHSO2Et
123	tBu	C(Me)OH	CH2	O	CH2NHSO2Et
124	tBu	C(O)	CH(Me)	O	CH2NHSO2Et
125	tBu	CHOH	CH(Me)	O	CH2NHSO2Et
126	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2Et
127	tBu	C(O)	CH2	O	CH2NHS(O)Et
128	tBu	CHOH	CH2	O	CH2NHS(O)Et
129	tBu	C(Me)OH	CH2	O	CH2NHS(O)Et
130	tBu	C(O)	CH(Me)	O	CH2NHS(O)Et
131	tBu	CHOH	CH(Me)	O	CH2NHS(O)Et
132	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)Et
133	tBu	C(O)	CH2	O	CH2NHSO2iPr
134	tBu	CHOH	CH2	O	CH2NHSO2iPr
135	tBu	C(Me)OH	CH2	O	CH2NHSO2iPr
136	tBu	C(O)	CH(Me)	O	CH2NHSO2iPr
137	tBu	CHOH	CH(Me)	O	CH2NHSO2iPr
138	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2iPr
139	tBu	C(O)	CH2	O	CH2NHS(O)iPr
140	tBu	CHOH	CH2	O	CH2NHS(O)iPr
141	tBu	C(Me)OH	CH2	O	CH2NHS(O)iPr
142	tBu	C(O)	CH(Me)	O	CH2NHS(O)iPr
143	tBu	CHOH	CH(Me)	O	CH2NHS(O)iPr
144	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)iPr
145	tBu	C(O)	CH2	O	CH2NHSO2tBu
146	tBu	CHOH	CH2	O	CH2NHSO2tBu
147	tBu	C(Me)OH	CH2	O	CH2NHSO2tBu
148	tBu	C(O)	CH(Me)	O	CH2NHSO2tBu
149	tBu	CHOH	CH(Me)	O	CH2NHSO2tBu
150	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2tBu
151	tBu	C(O)	CH2	O	CH2NHS(O)tBu

152	tBu	CHOH	CH2	O	CH2NHS(O)tBu
153	tBu	C(Me)OH	CH2	O	CH2NHS(O)tBu
154	tBu	C(O)	CH(Me)	O	CH2NHS(O)tBu
155	tBu	CHOH	CH(Me)	O	CH2NHS(O)tBu
156	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)tBu
157	tBu	C(O)	CH2	O	CH2-N-pyrrolidin-2-one
158	tBu	CHOH	CH2	O	CH2-N-pyrrolidin-2-one
159	tBu	C(Me)OH	CH2	O	CH2-N-pyrrolidin-2-one
160	tBu	C(O)	CH(Me)	O	CH2-N-pyrrolidin-2-one
161	tBu	CHOH	CH(Me)	O	CH2-N-pyrrolidin-2-one
162	tBu	C(Me)OH	CH(Me)	O	CH2-N-pyrrolidin-2-one
163	tBu	C(O)	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
164	tBu	CHOH	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
165	tBu	C(Me)OH	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
166	tBu	C(O)	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
167	tBu	CHOH	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
168	tBu	C(Me)OH	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
169	tBu	C(O)	CH2	O	CH2CO2Me
170	tBu	CHOH	CH2	O	CH2CO2Me
171	tBu	C(Me)OH	CH2	O	CH2CO2Me
172	tBu	C(O)	CH(Me)	O	CH2CO2Me
173	tBu	CHOH	CH(Me)	O	CH2CO2Me
174	tBu	C(Me)OH	CH(Me)	O	CH2CO2Me
175	tBu	C(O)	CH2	O	CH2CO2H
176	tBu	CHOH	CH2	O	CH2CO2H

177	tBu	C(Me)OH	CH2	O	CH2CO2H
178	tBu	C(O)	CH(Me)	O	CH2CO2H
179	tBu	CHOH	CH(Me)	O	CH2CO2H
180	tBu	C(Me)OH	CH(Me)	O	CH2CO2H
181	tBu	C(O)	CH2	O	CH2C(O)NH2
182	tBu	CHOH	CH2	O	CH2C(O)NH2
183	tBu	C(Me)OH	CH2	O	CH2C(O)NH2
184	tBu	C(O)	CH(Me)	O	CH2C(O)NH2
185	tBu	CHOH	CH(Me)	O	CH2C(O)NH2
186	tBu	C(Me)OH	CH(Me)	O	CH2C(O)NH2
187	tBu	C(O)	CH2	O	CH2C(O)NMe2
188	tBu	CHOH	CH2	O	CH2C(O)NMe2
189	tBu	C(Me)OH	CH2	O	CH2C(O)NMe2
190	tBu	C(O)	CH(Me)	O	CH2C(O)NMe2
191	tBu	CHOH	CH(Me)	O	CH2C(O)NMe2
192	tBu	C(Me)OH	CH(Me)	O	CH2C(O)NMe2
193	tBu	C(O)	CH2	O	CH2C(O)-N-pyrrolidine
194	tBu	CHOH	CH2	O	CH2C(O)-N-pyrrolidine
195	tBu	C(Me)OH	CH2	O	CH2C(O)-N-pyrrolidine
196	tBu	C(O)	CH(Me)	O	CH2C(O)-N-pyrrolidine
197	tBu	CHOH	CH(Me)	O	CH2C(O)-N-pyrrolidine
198	tBu	C(Me)OH	CH(Me)	O	CH2C(O)-N-pyrrolidine
199	tBu	C(O)	CH2	O	CH2-5-tetrazolyl
200	tBu	CHOH	CH2	O	CH2-5-tetrazolyl
201	tBu	C(Me)OH	CH2	O	CH2-5-tetrazolyl
202	tBu	C(O)	CH(Me)	O	CH2-5-tetrazolyl
203	tBu	CHOH	CH(Me)	O	CH2-5-tetrazolyl
204	tBu	C(Me)OH	CH(Me)	O	CH2-5-tetrazolyl
205	tBu	C(O)	CH2	O	C(O)C(O)OH
206	tBu	CHOH	CH2	O	C(O)C(O)OH
207	tBu	C(Me)OH	CH2	O	C(O)C(O)OH

208	tBu	C(O)	CH(Me)	O	C(O)C(O)OH
209	tBu	CHOH	CH(Me)	O	C(O)C(O)OH
210	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)OH
211	tBu	C(O)	CH2	O	CH(OH)C(O)OH
212	tBu	CHOH	CH2	O	CH(OH)C(O)OH
213	tBu	C(Me)OH	CH2	O	CH(OH)C(O)OH
214	tBu	C(O)	CH(Me)	O	CH(OH)C(O)OH
215	tBu	CHOH	CH(Me)	O	CH(OH)C(O)OH
216	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)OH
217	tBu	C(O)	CH2	O	C(O)C(O)NH2
218	tBu	CHOH	CH2	O	C(O)C(O)NH2
219	tBu	C(Me)OH	CH2	O	C(O)C(O)NH2
220	tBu	C(O)	CH(Me)	O	C(O)C(O)NH2
221	tBu	CHOH	CH(Me)	O	C(O)C(O)NH2
222	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)NH2
223	tBu	C(O)	CH2	O	CH(OH)C(O)NH2
224	tBu	CHOH	CH2	O	CH(OH)C(O)NH2
225	tBu	C(Me)OH	CH2	O	CH(OH)C(O)NH2
226	tBu	C(O)	CH(Me)	O	CH(OH)C(O)NH2
227	tBu	CHOH	CH(Me)	O	CH(OH)C(O)NH2
228	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)NH2
229	tBu	C(O)	CH2	O	C(O)C(O)NMe2
230	tBu	CHOH	CH2	O	C(O)C(O)NMe2
231	tBu	C(Me)OH	CH2	O	C(O)C(O)NMe2
232	tBu	C(O)	CH(Me)	O	C(O)C(O)NMe2
233	tBu	CHOH	CH(Me)	O	C(O)C(O)NMe2
234	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)NMe2
235	tBu	C(O)	CH2	O	CH(OH)C(O)NMe2
236	tBu	CHOH	CH2	O	CH(OH)C(O)NMe2
237	tBu	C(Me)OH	CH2	O	CH(OH)C(O)NMe2
238	tBu	C(O)	CH(Me)	O	CH(OH)C(O)NMe2

239	tBu	CHOH	CH(Me)	O	CH(OH)C(O)NMe2
240	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)NMe2
241	tBu	C(O)	CH2	O	CH2CH2CO2H
242	tBu	CHOH	CH2	O	CH2CH2CO2H
243	tBu	C(Me)OH	CH2	O	CH2CH2CO2H
244	tBu	C(O)	CH(Me)	O	CH2CH2CO2H
245	tBu	CHOH	CH(Me)	O	CH2CH2CO2H
246	tBu	C(Me)OH	CH(Me)	O	CH2CH2CO2H
247	tBu	C(O)	CH2	O	CH2CH2C(O)NH2
248	tBu	CHOH	CH2	O	CH2CH2C(O)NH2
249	tBu	C(Me)OH	CH2	O	CH2CH2C(O)NH2
250	tBu	C(O)	CH(Me)	O	CH2CH2C(O)NH2
251	tBu	CHOH	CH(Me)	O	CH2CH2C(O)NH2
252	tBu	C(Me)OH	CH(Me)	O	CH2CH2C(O)NH2
253	tBu	C(O)	CH2	O	CH2CH2C(O)NMe2
254	tBu	CHOH	CH2	O	CH2CH2C(O)NMe2
255	tBu	C(Me)OH	CH2	O	CH2CH2C(O)NMe2
256	tBu	C(O)	CH(Me)	O	CH2CH2C(O)NMe2
257	tBu	CHOH	CH(Me)	O	CH2CH2C(O)NMe2
258	tBu	C(Me)OH	CH(Me)	O	CH2CH2C(O)NMe2
259	tBu	C(O)	CH2	O	CH2CH2-5-tetrazolyl
260	tBu	CHOH	CH2	O	CH2CH2-5-tetrazolyl
261	tBu	C(Me)OH	CH2	O	CH2CH2-5-tetrazolyl
262	tBu	C(O)	CH(Me)	O	CH2CH2-5-tetrazolyl
263	tBu	CHOH	CH(Me)	O	CH2CH2-5-tetrazolyl
264	tBu	C(Me)OH	CH(Me)	O	CH2CH2-5-tetrazolyl
265	tBu	C(O)	CH2	O	CH2S(O)2Me
266	tBu	CHOH	CH2	O	CH2S(O)2Me
267	tBu	C(Me)OH	CH2	O	CH2S(O)2Me
268	tBu	C(O)	CH(Me)	O	CH2S(O)2Me
269	tBu	CHOH	CH(Me)	O	CH2S(O)2Me

270	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2Me
271	tBu	C(O)	CH2	O	CH2S(O)Me
272	tBu	CHOH	CH2	O	CH2S(O2Me
273	tBu	C(Me)OH	CH2	O	CH2S(O)Me
274	tBu	C(O)	CH(Me)	O	CH2S(O)Me
275	tBu	CHOH	CH(Me)	O	CH2S(O)Me
276	tBu	C(Me)OH	CH(Me)	O	CH2S(O)Me
277	tBu	C(O)	CH2	O	CH2CH2S(O)2Me
278	tBu	CHOH	CH2	O	CH2CH2S(O)2Me
279	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2Me
280	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2Me
281	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2Me
282	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2Me
283	tBu	C(O)	CH2	O	CH2CH2S(O)Me
284	tBu	CHOH	CH2	O	CH2CH2S(O)Me
285	tBu	C(Me)OH	CH2	O	CH2CH2S(O)Me
286	tBu	C(O)	CH(Me)	O	CH2CH2S(O)Me
287	tBu	CHOH	CH(Me)	O	CH2CH2S(O)Me
288	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)Me
289	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2Me
290	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2Me
291	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2Me
292	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2Me
293	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2Me
294	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2Me
295	tBu	C(O)	CH2	O	CH2CH2CH2S(O)Me
296	tBu	CHOH	CH2	O	CH2CH2CH2S(O)Me
297	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)Me
298	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)Me
299	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)Me
300	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)Me

301	tBu	C(O)	CH2	O	CH2S(O)2Et
302	tBu	CHOH	CH2	O	CH2S(O)2Et
303	tBu	C(Me)OH	CH2	O	CH2S(O)2Et
304	tBu	C(O)	CH(Me)	O	CH2S(O)2Et
305	tBu	CHOH	CH(Me)	O	CH2S(O)2Et
306	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2Et
307	tBu	C(O)	CH2	O	CH2S(O)Et
308	tBu	CHOH	CH2	O	CH2S(O)Et
309	tBu	C(Me)OH	CH2	O	CH2S(O)Et
310	tBu	C(O)	CH(Me)	O	CH2S(O)Et
311	tBu	CHOH	CH(Me)	O	CH2S(O)Et
312	tBu	C(Me)OH	CH(Me)	O	CH2S(O)Et
313	tBu	C(O)	CH2	O	CH2CH2S(O)2Et
314	tBu	CHOH	CH2	O	CH2CH2S(O)2Et
315	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2Et
316	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2Et
317	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2Et
318	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2Et
319	tBu	C(O)	CH2	O	CH2CH2S(O)Et
320	tBu	CHOH	CH2	O	CH2CH2S(O)Et
321	tBu	C(Me)OH	CH2	O	CH2CH2S(O)Et
322	tBu	C(O)	CH(Me)	O	CH2CH2S(O)Et
323	tBu	CHOH	CH(Me)	O	CH2CH2S(O)Et
324	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)Et
325	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2Et
326	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2Et
327	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2Et
328	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2Et
329	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2Et
330	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2Et
331	tBu	C(O)	CH2	O	CH2CH2CH2S(O)Et

332	tBu	CHOH	CH2	O	CH2CH2CH2S(O)Et
333	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)Et
334	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)Et
335	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)Et
336	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)Et
337	tBu	C(O)	CH2	O	CH2S(O)2iPr
338	tBu	CHOH	CH2	O	CH2S(O)2iPr
339	tBu	C(Me)OH	CH2	O	CH2S(O)2iPr
340	tBu	C(O)	CH(Me)	O	CH2S(O)2iPr
341	tBu	CHOH	CH(Me)	O	CH2S(O)2iPr
342	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2iPr
343	tBu	C(O)	CH2	O	CH2S(O)iPr
344	tBu	CHOH	CH2	O	CH2S(O)iPr
345	tBu	C(Me)OH	CH2	O	CH2S(O)iPr
346	tBu	C(O)	CH(Me)	O	CH2S(O)iPr
347	tBu	CHOH	CH(Me)	O	CH2S(O)iPr
348	tBu	C(Me)OH	CH(Me)	O	CH2S(O)iPr
349	tBu	C(O)	CH2	O	CH2CH2S(O)2iPr
350	tBu	CHOH	CH2	O	CH2CH2S(O)2iPr
351	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2iPr
352	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2iPr
353	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2iPr
354	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2iPr
355	tBu	C(O)	CH2	O	CH2CH2S(O)iPr
356	tBu	CHOH	CH2	O	CH2CH2S(O)iPr
357	tBu	C(Me)OH	CH2	O	CH2CH2S(O)iPr
358	tBu	C(O)	CH(Me)	O	CH2CH2S(O)iPr
359	tBu	CHOH	CH(Me)	O	CH2CH2S(O)iPr
360	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)iPr
361	tBu	C(O)	CH2	O	CH2S(O)2tBu
362	tBu	CHOH	CH2	O	CH2S(O)2tBu

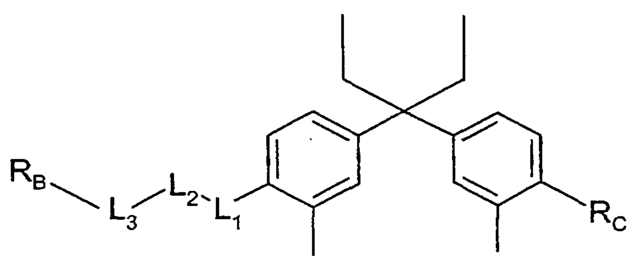
363	tBu	C(Me)OH	CH2	O	CH2S(O)2tBu
364	tBu	C(O)	CH(Me)	O	CH2S(O)2tBu
365	tBu	CHOH	CH(Me)	O	CH2S(O)2tBu
366	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2tBu
367	tBu	C(O)	CH2	O	CH2S(O)tBu
368	tBu	CHOH	CH2	O	CH2S(O)tBu
369	tBu	C(Me)OH	CH2	O	CH2S(O)tBu
370	tBu	C(O)	CH(Me)	O	CH2S(O)tBu
371	tBu	CHOH	CH(Me)	O	CH2S(O)tBu
372	tBu	C(Me)OH	CH(Me)	O	CH2S(O)tBu
373	tBu	C(O)	CH2	O	CH2CH2S(O)2tBu
374	tBu	CHOH	CH2	O	CH2CH2S(O)2tBu
375	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2tBu
376	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2tBu
377	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2tBu
378	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2tBu
379	tBu	C(O)	CH2	O	CH2CH2S(O)tBu
380	tBu	CHOH	CH2	O	CH2CH2S(O)tBu
381	tBu	C(Me)OH	CH2	O	CH2CH2S(O)tBu
382	tBu	C(O)	CH(Me)	O	CH2CH2S(O)tBu
383	tBu	CHOH	CH(Me)	O	CH2CH2S(O)tBu
384	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)tBu
385	tBu	C(O)	CH2	O	CH2CH2S(O)2NH2
386	tBu	CHOH	CH2	O	CH2CH2S(O)2NH2
387	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2NH2
388	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2NH2
389	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2NH2
390	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2NH2
391	tBu	C(O)	CH2	O	CH2CH2S(O)NH2
392	tBu	CHOH	CH2	O	CH2CH2S(O)NH2
393	tBu	C(Me)OH	CH2	O	CH2CH2S(O)NH2

394	tBu	C(O)	CH(Me)	O	CH2CH2S(O)NH2
395	tBu	CHOH	CH(Me)	O	CH2CH2S(O)NH2
396	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)NH2
397	tBu	C(O)	CH2	O	CH2CH2S(O)2NMe2
398	tBu	CHOH	CH2	O	CH2CH2S(O)2NMe2
399	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2NMe2
400	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2NMe2
401	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2NMe2
402	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2NMe2
403	tBu	C(O)	CH2	O	CH2CH2S(O)NMe2
404	tBu	CHOH	CH2	O	CH2CH2S(O)NMe2
405	tBu	C(Me)OH	CH2	O	CH2CH2S(O)NMe2
406	tBu	C(O)	CH(Me)	O	CH2CH2S(O)NMe2
407	tBu	CHOH	CH(Me)	O	CH2CH2S(O)NMe2
408	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)NMe2
409	tBu	C(O)	CH2	O	C(O)CH2S(O)2Me
410	tBu	CHOH	CH2	O	C(O)CH2S(O)2Me
411	tBu	C(Me)OH	CH2	O	C(O)CH2S(O)2Me
412	tBu	C(O)	CH(Me)	O	C(O)CH2S(O)2Me
413	tBu	CHOH	CH(Me)	O	C(O)CH2S(O)2Me
414	tBu	C(Me)OH	CH(Me)	O	C(O)CH2S(O)2Me
415	tBu	C(O)	CH2	O	C(O)CH2S(O)Me
416	tBu	CHOH	CH2	O	C(O)CH2S(O)Me
417	tBu	C(Me)OH	CH2	O	C(O)CH2S(O)Me
418	tBu	C(O)	CH(Me)	O	C(O)CH2S(O)Me
419	tBu	CHOH	CH(Me)	O	C(O)CH2S(O)Me
420	tBu	C(Me)OH	CH(Me)	O	C(O)CH2S(O)Me
421	tBu	C(O)	CH2	O	C(O)CH2CH2S(O)2Me
422	tBu	CHOH	CH2	O	C(O)CH2CH2S(O)2Me
423	tBu	C(Me)OH	CH2	O	C(O)CH2CH2S(O)2Me
424	tBu	C(O)	CH(Me)	O	C(O)CH2CH2S(O)2Me

425	tBu	CHOH	CH(Me)	O	C(O)CH2CH2S(O)2Me
426	tBu	C(Me)OH	CH(Me)	O	C(O)CH2CH2S(O)2Me
427	tBu	C(O)	CH2	O	C(O)CH2CH2S(O)Me
428	tBu	CHOH	CH2	O	C(O)CH2CH2S(O)Me
429	tBu	C(Me)OH	CH2	O	C(O)CH2CH2S(O)Me
430	tBu	C(O)	CH(Me)	O	C(O)CH2CH2S(O)Me
431	tBu	CHOH	CH(Me)	O	C(O)CH2CH2S(O)Me
432	tBu	C(Me)OH	CH(Me)	O	C(O)CH2CH2S(O)Me
433	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2NH2
434	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2NH2
435	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2NH2
436	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2NH2
437	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2NH2
438	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2NH2
439	tBu	C(O)	CH2	O	CH2CH2CH2S(O)NH2
440	tBu	CHOH	CH2	O	CH2CH2CH2S(O)NH2
441	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)NH2
442	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)NH2
443	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)NH2
444	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)NH2
445	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
446	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
447	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
448	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
449	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
450	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
451	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
452	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
453	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
454	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
455	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl

456	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
457	tBu	C(O)	CH2	CH2	imidazolidine-2,4-dione-5-yl
458	tBu	CHOH	CH2	CH2	imidazolidine-2,4-dione-5-yl
459	tBu	C(Me)OH	CH2	CH2	imidazolidine-2,4-dione-5-yl
460	tBu	C(O)	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
461	tBu	CHOH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
462	tBu	C(Me)OH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
463	tBu	C(O)	CH2	CH2	isoxazol-3-ol-5-yl
464	tBu	CHOH	CH2	CH2	isoxazol-3-ol-5-yl
465	tBu	C(Me)OH	CH2	CH2	isoxazol-3-ol-5-yl
466	tBu	C(O)	CH(Me)	CH2	isoxazol-3-ol-5-yl
467	tBu	CHOH	CH(Me)	CH2	isoxazol-3-ol-5-yl
468	tBu	C(Me)OH	CH(Me)	CH2	isoxazol-3-ol-5-yl

Among other preferred compounds of the invention are also those represented by the formula:



and pharmaceutically acceptable salts thereof; wherein;
said compound is selected from a compound code numbered 1A thru 468A, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the row following the compound code number, as set out in the following Table 2 :

Table 2

	R_B	L_3	L_2	L_1	R_C
1A	tBu	C(O)	CH2	CH2	C(O)CH(Me)CH2CO2H
2A	tBu	CHOH	CH2	CH2	C(O)CH(Me)CH2CO2H
3A	tBu	C(Me)OH	CH2	CH2	C(O)CH(Me)CH2CO2H

4A	tBu	C(O)	CH(Me)	CH2	C(O)CH(Me)CH2CO2H
5A	tBu	CHOH	CH(Me)	CH2	C(O)CH(Me)CH2CO2H
6A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH(Me)CH2CO2H
7A	tBu	C(O)	CH2	CH2	CO2H
8A	tBu	CHOH	CH2	CH2	CO2H
9A	tBu	C(Me)OH	CH2	CH2	CO2H
10A	tBu	C(O)	CH(Me)	CH2	CO2H
11A	tBu	CHOH	CH(Me)	CH2	CO2H
12A	tBu	C(Me)OH	CH(Me)	CH2	CO2H
13A	tBu	C(O)	CH2	CH2	C(O)NH2
14A	tBu	CHOH	CH2	CH2	C(O)NH2
15A	tBu	C(Me)OH	CH2	CH2	C(O)NH2
16A	tBu	C(O)	CH(Me)	CH2	C(O)NH2
17A	tBu	CHOH	CH(Me)	CH2	C(O)NH2
18A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NH2
19A	tBu	C(O)	CH2	CH2	C(O)NMe2
20A	tBu	CHOH	CH2	CH2	C(O)NMe2
21A	tBu	C(Me)OH	CH2	CH2	C(O)NMe2
22A	tBu	C(O)	CH(Me)	CH2	C(O)NMe2
23A	tBu	CHOH	CH(Me)	CH2	C(O)NMe2
24A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NMe2
25A	tBu	C(O)	CH2	CH2	5-tetrazolyl
26A	tBu	CHOH	CH2	CH2	5-tetrazolyl
27A	tBu	C(Me)OH	CH2	CH2	5-tetrazolyl
28A	tBu	C(O)	CH(Me)	CH2	5-tetrazolyl
29A	tBu	CHOH	CH(Me)	CH2	5-tetrazolyl
30A	tBu	C(Me)OH	CH(Me)	CH2	5-tetrazolyl
31A	tBu	C(O)	CH2	CH2	C(O)-NH-5-tetrazolyl
32A	tBu	CHOH	CH2	CH2	C(O)-NH-5-tetrazolyl
33A	tBu	C(Me)OH	CH2	CH2	C(O)-NH-5-tetrazolyl
34A	tBu	C(O)	CH(Me)	CH2	C(O)-NH-5-tetrazolyl

35A	tBu	CHOH	CH(Me)	CH2	C(O)-NH-5-tetrazolyl
36A	tBu	C(Me)OH	CH(Me)	CH2	C(O)-NH-5-tetrazolyl
37A	tBu	C(O)	CH2	CH2	C(O)NHCH2SO2Me
38A	tBu	CHOH	CH2	CH2	C(O)NHCH2SO2Me
39A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2SO2Me
40A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2SO2Me
41A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2SO2Me
42A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2SO2Me
43A	tBu	C(O)	CH2	CH2	C(O)NHCH2S(O)Me
44A	tBu	CHOH	CH2	CH2	C(O)NHCH2S(O)Me
45A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2S(O)Me
46A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2S(O)Me
47A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2S(O)Me
48A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2S(O)Me
49A	tBu	C(O)	CH2	CH2	C(O)NHCH2CH2SO2Me
50A	tBu	CHOH	CH2	CH2	C(O)NHCH2CH2SO2Me
51A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2CH2SO2Me
52A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2CH2SO2Me
53A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2CH2SO2Me
54A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2CH2SO2Me
55A	tBu	C(O)	CH2	CH2	C(O)NHCH2CH2S(O)Me
56A	tBu	CHOH	CH2	CH2	C(O)NHCH2CH2S(O)Me
57A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2CH2S(O)Me
58A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
59A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
60A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
61A	tBu	C(O)	CH2	CH2	C(O)NHSO2Me
62A	tBu	CHOH	CH2	CH2	C(O)NHSO2Me
63A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2Me
64A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2Me
65A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2Me

66A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2Me
67A	tBu	C(O)	CH2	CH2	C(O)NHS(O)Me
68A	tBu	CHOH	CH2	CH2	C(O)NHS(O)Me
69A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)Me
70A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)Me
71A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)Me
72A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)Me
73A	tBu	C(O)	CH2	CH2	C(O)NHSO2Et
74A	tBu	CHOH	CH2	CH2	C(O)NHSO2Et
75A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2Et
76A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2Et
77A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2Et
78A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2Et
79A	tBu	C(O)	CH2	CH2	C(O)NHS(O)Et
80A	tBu	CHOH	CH2	CH2	C(O)NHS(O)Et
81A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)Et
82A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)Et
83A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)Et
84A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)Et
85A	tBu	C(O)	CH2	CH2	C(O)NHSO2iPr
86A	tBu	CHOH	CH2	CH2	C(O)NHSO2iPr
87A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2iPr
88A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2iPr
89A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2iPr
90A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2iPr
91A	tBu	C(O)	CH2	CH2	C(O)NHS(O)iPr
92A	tBu	CHOH	CH2	CH2	C(O)NHS(O)iPr
93A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)iPr
94A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)iPr
95A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)iPr
96A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)iPr

97A	tBu	C(O)	CH2	CH2	C(O)NHSO2tBu
98A	tBu	CHOH	CH2	CH2	C(O)NHSO2tBu
99A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2tBu
100A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2tBu
101A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2tBu
102A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2tBu
103A	tBu	C(O)	CH2	CH2	C(O)NHS(O)tBu
104A	tBu	CHOH	CH2	CH2	C(O)NHS(O)tBu
105A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)tBu
106A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)tBu
107A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)tBu
108A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)tBu
109A	tBu	C(O)	CH2	CH2	CH2NHSO2Me
110A	tBu	CHOH	CH2	CH2	CH2NHSO2Me
111A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2Me
112A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2Me
113A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2Me
114A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2Me
115A	tBu	C(O)	CH2	CH2	CH2NHS(O)Me
116A	tBu	CHOH	CH2	CH2	CH2NHS(O)Me
117A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)Me
118A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)Me
119A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)Me
120A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)Me
121A	tBu	C(O)	CH2	CH2	CH2NHSO2Et
122A	tBu	CHOH	CH2	CH2	CH2NHSO2Et
123A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2Et
124A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2Et
125A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2Et
126A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2Et
127A	tBu	C(O)	CH2	CH2	CH2NHS(O)Et

128A	tBu	CHOH	CH2	CH2	CH2NHS(O)Et
129A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)Et
130A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)Et
131A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)Et
132A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)Et
133A	tBu	C(O)	CH2	CH2	CH2NHSO2iPr
134A	tBu	CHOH	CH2	CH2	CH2NHSO2iPr
135A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2iPr
136A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2iPr
137A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2iPr
138A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2iPr
139A	tBu	C(O)	CH2	CH2	CH2NHS(O)iPr
140A	tBu	CHOH	CH2	CH2	CH2NHS(O)iPr
141A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)iPr
142A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)iPr
143A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)iPr
144A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)iPr
145A	tBu	C(O)	CH2	CH2	CH2NHSO2tBu
146A	tBu	CHOH	CH2	CH2	CH2NHSO2tBu
147A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2tBu
148A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2tBu
149A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2tBu
150A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2tBu
151A	tBu	C(O)	CH2	CH2	CH2NHS(O)tBu
152A	tBu	CHOH	CH2	CH2	CH2NHS(O)tBu
153A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)tBu
154A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)tBu
155A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)tBu
156A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)tBu
157A	tBu	C(O)	CH2	CH2	CH2-N-pyrrolidin-2-one
158A	tBu	CHOH	CH2	CH2	CH2-N-pyrrolidin-2-one

159A	tBu	C(Me)OH	CH2	CH2	CH2-N-pyrrolidin-2-one
160A	tBu	C(O)	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
161A	tBu	CHOH	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
162A	tBu	C(Me)OH	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
163A	tBu	C(O)	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
164A	tBu	CHOH	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
165A	tBu	C(Me)OH	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
166A	tBu	C(O)	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
167A	tBu	CHOH	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
168A	tBu	C(Me)OH	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
169A	tBu	C(O)	CH2	CH2	CH2CO2Me
170A	tBu	CHOH	CH2	CH2	CH2CO2Me
171A	tBu	C(Me)OH	CH2	CH2	CH2CO2Me
172A	tBu	C(O)	CH(Me)	CH2	CH2CO2Me
173A	tBu	CHOH	CH(Me)	CH2	CH2CO2Me
174A	tBu	C(Me)OH	CH(Me)	CH2	CH2CO2Me
175A	tBu	C(O)	CH2	CH2	CH2CO2H
176A	tBu	CHOH	CH2	CH2	CH2CO2H
177A	tBu	C(Me)OH	CH2	CH2	CH2CO2H
178A	tBu	C(O)	CH(Me)	CH2	CH2CO2H
179A	tBu	CHOH	CH(Me)	CH2	CH2CO2H
180A	tBu	C(Me)OH	CH(Me)	CH2	CH2CO2H
181A	tBu	C(O)	CH2	CH2	CH2C(O)NH2
182A	tBu	CHOH	CH2	CH2	CH2C(O)NH2
183A	tBu	C(Me)OH	CH2	CH2	CH2C(O)NH2

184A	tBu	C(O)	CH(Me)	CH2	CH2C(O)NH2
185A	tBu	CHOH	CH(Me)	CH2	CH2C(O)NH2
186A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)NH2
187A	tBu	C(O)	CH2	CH2	CH2C(O)NMe2
188A	tBu	CHOH	CH2	CH2	CH2C(O)NMe2
189A	tBu	C(Me)OH	CH2	CH2	CH2C(O)NMe2
190A	tBu	C(O)	CH(Me)	CH2	CH2C(O)NMe2
191A	tBu	CHOH	CH(Me)	CH2	CH2C(O)NMe2
192A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)NMe2
193A	tBu	C(O)	CH2	CH2	CH2C(O)-N-pyrrolidine
194A	tBu	CHOH	CH2	CH2	CH2C(O)-N-pyrrolidine
195A	tBu	C(Me)OH	CH2	CH2	CH2C(O)-N-pyrrolidine
196A	tBu	C(O)	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
197A	tBu	CHOH	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
198A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
199A	tBu	C(O)	CH2	CH2	CH2-5-tetrazolyl
200A	tBu	CHOH	CH2	CH2	CH2-5-tetrazolyl
201A	tBu	C(Me)OH	CH2	CH2	CH2-5-tetrazolyl
202A	tBu	C(O)	CH(Me)	CH2	CH2-5-tetrazolyl
203A	tBu	CHOH	CH(Me)	CH2	CH2-5-tetrazolyl
204A	tBu	C(Me)OH	CH(Me)	CH2	CH2-5-tetrazolyl
205A	tBu	C(O)	CH2	CH2	C(O)C(O)OH
206A	tBu	CHOH	CH2	CH2	C(O)C(O)OH
207A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)OH
208A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)OH
209A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)OH
210A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)OH
211A	tBu	C(O)	CH2	CH2	CH(OH)C(O)OH
212A	tBu	CHOH	CH2	CH2	CH(OH)C(O)OH
213A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)OH
214A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)OH

215A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)OH
216A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)OH
217A	tBu	C(O)	CH2	CH2	C(O)C(O)NH2
218A	tBu	CHOH	CH2	CH2	C(O)C(O)NH2
219A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)NH2
220A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)NH2
221A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)NH2
222A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)NH2
223A	tBu	C(O)	CH2	CH2	CH(OH)C(O)NH2
224A	tBu	CHOH	CH2	CH2	CH(OH)C(O)NH2
225A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)NH2
226A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)NH2
227A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)NH2
228A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)NH2
229A	tBu	C(O)	CH2	CH2	C(O)C(O)NMe2
230A	tBu	CHOH	CH2	CH2	C(O)C(O)NMe2
231A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)NMe2
232A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)NMe2
233A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)NMe2
234A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)NMe2
235A	tBu	C(O)	CH2	CH2	CH(OH)C(O)NMe2
236A	tBu	CHOH	CH2	CH2	CH(OH)C(O)NMe2
237A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)NMe2
238A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)NMe2
239A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)NMe2
240A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)NMe2
241A	tBu	C(O)	CH2	CH2	CH2CH2CO2H
242A	tBu	CHOH	CH2	CH2	CH2CH2CO2H
243A	tBu	C(Me)OH	CH2	CH2	CH2CH2CO2H
244A	tBu	C(O)	CH(Me)	CH2	CH2CH2CO2H
245A	tBu	CHOH	CH(Me)	CH2	CH2CH2CO2H

246A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CO2H
247A	tBu	C(O)	CH2	CH2	CH2CH2C(O)NH2
248A	tBu	CHOH	CH2	CH2	CH2CH2C(O)NH2
249A	tBu	C(Me)OH	CH2	CH2	CH2CH2C(O)NH2
250A	tBu	C(O)	CH(Me)	CH2	CH2CH2C(O)NH2
251A	tBu	CHOH	CH(Me)	CH2	CH2CH2C(O)NH2
252A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2C(O)NH2
253A	tBu	C(O)	CH2	CH2	CH2CH2C(O)NMe2
254A	tBu	CHOH	CH2	CH2	CH2CH2C(O)NMe2
255A	tBu	C(Me)OH	CH2	CH2	CH2CH2C(O)NMe2
256A	tBu	C(O)	CH(Me)	CH2	CH2CH2C(O)NMe2
257A	tBu	CHOH	CH(Me)	CH2	CH2CH2C(O)NMe2
258A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2C(O)NMe2
259A	tBu	C(O)	CH2	CH2	CH2CH2-5-tetrazolyl
260A	tBu	CHOH	CH2	CH2	CH2CH2-5-tetrazolyl
261A	tBu	C(Me)OH	CH2	CH2	CH2CH2-5-tetrazolyl
262A	tBu	C(O)	CH(Me)	CH2	CH2CH2-5-tetrazolyl
263A	tBu	CHOH	CH(Me)	CH2	CH2CH2-5-tetrazolyl
264A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2-5-tetrazolyl
265A	tBu	C(O)	CH2	CH2	CH2S(O)2Me
266A	tBu	CHOH	CH2	CH2	CH2S(O)2Me
267A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2Me
268A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2Me
269A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2Me
270A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2Me
271A	tBu	C(O)	CH2	CH2	CH2S(O)Me
272A	tBu	CHOH	CH2	CH2	CH2S(O2Me
273A	tBu	C(Me)OH	CH2	CH2	CH2S(O)Me
274A	tBu	C(O)	CH(Me)	CH2	CH2S(O)Me
275A	tBu	CHOH	CH(Me)	CH2	CH2S(O)Me
276A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)Me

277A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2Me
278A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2Me
279A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2Me
280A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2Me
281A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2Me
282A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2Me
283A	tBu	C(O)	CH2	CH2	CH2CH2S(O)Me
284A	tBu	CHOH	CH2	CH2	CH2CH2S(O)Me
285A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)Me
286A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)Me
287A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)Me
288A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)Me
289A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2Me
290A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2Me
291A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2Me
292A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2Me
293A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2Me
294A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2Me
295A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)Me
296A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)Me
297A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)Me
298A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)Me
299A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)Me
300A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)Me
301A	tBu	C(O)	CH2	CH2	CH2S(O)2Et
302A	tBu	CHOH	CH2	CH2	CH2S(O)2Et
303A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2Et
304A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2Et
305A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2Et
306A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2Et
307A	tBu	C(O)	CH2	CH2	CH2S(O)Et

308A	tBu	CHOH	CH2	CH2	CH2S(O)Et
309A	tBu	C(Me)OH	CH2	CH2	CH2S(O)Et
310A	tBu	C(O)	CH(Me)	CH2	CH2S(O)Et
311A	tBu	CHOH	CH(Me)	CH2	CH2S(O)Et
312A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)Et
313A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2Et
314A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2Et
315A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2Et
316A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2Et
317A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2Et
318A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2Et
319A	tBu	C(O)	CH2	CH2	CH2CH2S(O)Et
320A	tBu	CHOH	CH2	CH2	CH2CH2S(O)Et
321A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)Et
322A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)Et
323A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)Et
324A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)Et
325A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2Et
326A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2Et
327A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2Et
328A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2Et
329A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2Et
330A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2Et
331A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)Et
332A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)Et
333A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)Et
334A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)Et
335A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)Et
336A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)Et
337A	tBu	C(O)	CH2	CH2	CH2S(O)2iPr
338A	tBu	CHOH	CH2	CH2	CH2S(O)2iPr

339A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2iPr
340A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2iPr
341A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2iPr
342A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2iPr
343A	tBu	C(O)	CH2	CH2	CH2S(O)iPr
344A	tBu	CHOH	CH2	CH2	CH2S(O)iPr
345A	tBu	C(Me)OH	CH2	CH2	CH2S(O)iPr
346A	tBu	C(O)	CH(Me)	CH2	CH2S(O)iPr
347A	tBu	CHOH	CH(Me)	CH2	CH2S(O)iPr
348A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)iPr
349A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2iPr
350A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2iPr
351A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2iPr
352A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2iPr
353A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2iPr
354A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2iPr
355A	tBu	C(O)	CH2	CH2	CH2CH2S(O)iPr
356A	tBu	CHOH	CH2	CH2	CH2CH2S(O)iPr
357A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)iPr
358A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)iPr
359A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)iPr
360A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)iPr
361A	tBu	C(O)	CH2	CH2	CH2S(O)2tBu
362A	tBu	CHOH	CH2	CH2	CH2S(O)2tBu
363A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2tBu
364A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2tBu
365A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2tBu
366A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2tBu
367A	tBu	C(O)	CH2	CH2	CH2S(O)tBu
368A	tBu	CHOH	CH2	CH2	CH2S(O)tBu
369A	tBu	C(Me)OH	CH2	CH2	CH2S(O)tBu

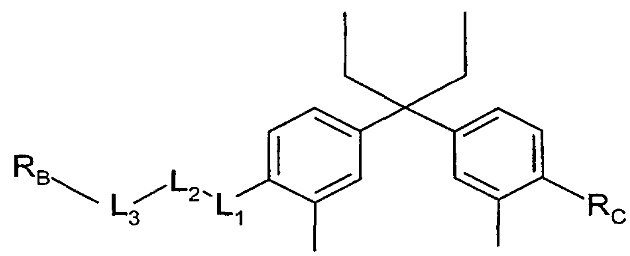
370A	tBu	C(O)	CH(Me)	CH2	CH2S(O)tBu
371A	tBu	CHOH	CH(Me)	CH2	CH2S(O)tBu
372A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)tBu
373A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2tBu
374A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2tBu
375A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2tBu
376A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2tBu
377A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2tBu
378A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2tBu
379A	tBu	C(O)	CH2	CH2	CH2CH2S(O)tBu
380A	tBu	CHOH	CH2	CH2	CH2CH2S(O)tBu
381A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)tBu
382A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)tBu
383A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)tBu
384A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)tBu
385A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2NH2
386A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2NH2
387A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2NH2
388A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2NH2
389A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2NH2
390A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2NH2
391A	tBu	C(O)	CH2	CH2	CH2CH2S(O)NH2
392A	tBu	CHOH	CH2	CH2	CH2CH2S(O)NH2
393A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)NH2
394A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)NH2
395A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)NH2
396A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)NH2
397A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2NMe2
398A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2NMe2
399A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2NMe2
400A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2NMe2

401A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2NMe2
402A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2NMe2
403A	tBu	C(O)	CH2	CH2	CH2CH2S(O)NMe2
404A	tBu	CHOH	CH2	CH2	CH2CH2S(O)NMe2
405A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)NMe2
406A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)NMe2
407A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)NMe2
408A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)NMe2
409A	tBu	C(O)	CH2	CH2	C(O)CH2S(O)2Me
410A	tBu	CHOH	CH2	CH2	C(O)CH2S(O)2Me
411A	tBu	C(Me)OH	CH2	CH2	C(O)CH2S(O)2Me
412A	tBu	C(O)	CH(Me)	CH2	C(O)CH2S(O)2Me
413A	tBu	CHOH	CH(Me)	CH2	C(O)CH2S(O)2Me
414A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2S(O)2Me
415A	tBu	C(O)	CH2	CH2	C(O)CH2S(O)Me
416A	tBu	CHOH	CH2	CH2	C(O)CH2S(O)Me
417A	tBu	C(Me)OH	CH2	CH2	C(O)CH2S(O)Me
418A	tBu	C(O)	CH(Me)	CH2	C(O)CH2S(O)Me
419A	tBu	CHOH	CH(Me)	CH2	C(O)CH2S(O)Me
420A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2S(O)Me
421A	tBu	C(O)	CH2	CH2	C(O)CH2CH2S(O)2Me
422A	tBu	CHOH	CH2	CH2	C(O)CH2CH2S(O)2Me
423A	tBu	C(Me)OH	CH2	CH2	C(O)CH2CH2S(O)2Me
424A	tBu	C(O)	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
425A	tBu	CHOH	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
426A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
427A	tBu	C(O)	CH2	CH2	C(O)CH2CH2S(O)Me
428A	tBu	CHOH	CH2	CH2	C(O)CH2CH2S(O)Me
429A	tBu	C(Me)OH	CH2	CH2	C(O)CH2CH2S(O)Me
430A	tBu	C(O)	CH(Me)	CH2	C(O)CH2CH2S(O)Me
431A	tBu	CHOH	CH(Me)	CH2	C(O)CH2CH2S(O)Me

432A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2CH2S(O)Me
433A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2NH2
434A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2NH2
435A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2NH2
436A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
437A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
438A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
439A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)NH2
440A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)NH2
441A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)NH2
442A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)NH2
443A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)NH2
444A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)NH2
445A	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
446A	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
447A	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
448A	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
449A	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
450A	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
451A	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
452A	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
453A	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
454A	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
455A	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
456A	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
457A	tBu	C(O)	CH2	CH2	imidazolidine-2,4-dione-5-yl
458A	tBu	CHOH	CH2	CH2	imidazolidine-2,4-dione-5-yl
459A	tBu	C(Me)OH	CH2	CH2	imidazolidine-2,4-dione-5-yl
460A	tBu	C(O)	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
461A	tBu	CHOH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
462A	tBu	C(Me)OH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl

463A	tBu	C(O)	CH2	CH2	isoxazol-3-ol-5-yl
464A	tBu	CHOH	CH2	CH2	isoxazol-3-ol-5-yl
465A	tBu	C(Me)OH	CH2	CH2	isoxazol-3-ol-5-yl
466A	tBu	C(O)	CH(Me)	CH2	isoxazol-3-ol-5-yl
467A	tBu	CHOH	CH(Me)	CH2	isoxazol-3-ol-5-yl
468A	tBu	C(Me)OH	CH(Me)	CH2	isoxazol-3-ol-5-yl

Among other preferred compounds of the invention are also those represented by the formula:



and pharmaceutically acceptable salts thereof;

wherein;

said compound is selected from a compound code numbered 1B thru 81B, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown

in the row following the compound code number, as set out in the following Table 3 :

Table 3

	R_B	L_3	L_2	L_1	R_C
1B	tBu	C(O)	CH2	O	-C(O)NH-CH_2-C(O)OH
2B	tBu	CHOH	CH2	O	-C(O)NH-CH_2-C(O)OH
3B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH_2-C(O)OH
4B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
5B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
6B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
7B	tBu	C(O)	CH2	O	-C(O)NH-CH(Me)-C(O)OH
8B	tBu	CHOH	CH2	O	-C(O)NH-CH(Me)-C(O)OH

9B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
10B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
11B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
12B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
13B	tBu	C(O)	CH2	O	-C(O)NH-CH(Et)-C(O)OH
14B	tBu	CHOH	CH2	O	-C(O)NH-CH(Et)-C(O)OH
15B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Et)-C(O)OH
16B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
17B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
18B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
19B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
20B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
21B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
22B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
23B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
24B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
25B	tBu	C(O)	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
26B	tBu	CHOH	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
27B	tBu	C(Me)OH	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
28B	tBu	C(O)	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH
29B	tBu	CHOH	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH
30B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH
31B	tBu	C(O)	CH2	O	-C(O)NH-CH(F)-C(O)OH
32B	tBu	CHOH	CH2	O	-C(O)NH-CH(F)-C(O)OH
33B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(F)-C(O)OH
34B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
35B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
36B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
37B	tBu	C(O)	CH2	O	-C(O)NH-CH(CF$_3$)-C(O)OH
38B	tBu	CHOH	CH2	O	-C(O)NH-CH(CF$_3$)-C(O)OH
39B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(CF$_3$)-C(O)OH

40B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
41B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
42B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
43B	tBu	C(O)	CH2	O	-C(O)NH-CH(OH)-C(O)OH
44B	tBu	CHOH	CH2	O	-C(O)NH-CH(OH)-C(O)OH
45B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(OH)-C(O)OH
46B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
47B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
48B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
49B	tBu	C(O)	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
50B	tBu	CHOH	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
51B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
52B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
53B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
54B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
55B	tBu	C(O)	CH2	O	-C(O)NH-CH(Me)-C(O)OH
56B	tBu	CHOH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
57B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
58B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
59B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
60B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
61B	tBu	C(O)	CH2	O	-C(O)NH-C($Me)_2$-C(O)OH
62B	tBu	CHOH	CH2	O	-C(O)NH-C($Me)_2$-C(O)OH
63B	tBu	C(Me)OH	CH2	O	-C(O)NH-C($Me)_2$-C(O)OH
64B	tBu	C(O)	CH(Me)	O	-C(O)NH-C($Me)_2$-C(O)OH
65B	tBu	CHOH	CH(Me)	O	-C(O)NH-C($Me)_2$-C(O)OH
66B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C($Me)_2$-C(O)OH
67B	tBu	C(O)	CH2	O	-C(O)NH-CF(Me)-C(O)OH
68B	tBu	CHOH	CH2	O	-C(O)NH-CF(Me)-C(O)OH
69B	tBu	C(Me)OH	CH2	O	-C(O)NH-CF(Me)-C(O)OH
70B	tBu	C(O)	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH

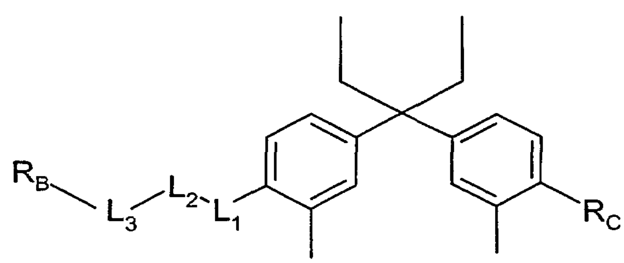
71B	tBu	CHOH	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH
72B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH
73B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
74B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
75B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
76B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
77B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
78B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)(CF_3)-C(O)OH
79B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
80B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
81B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
82B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
83B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
84B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
85B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
86B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
87B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
88B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
89B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
90B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)(cyclopropyl)CO_2H
91B	tBu	C(O)	CH2	O	-C(O)NMe-CH_2-C(O)OH
92B	tBu	CHOH	CH2	O	-C(O)NMe-CH_2-C(O)OH
93B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH_2-C(O)OH
94B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH
95B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH

96B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH
97B	tBu	C(O)	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
98B	tBu	CHOH	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
99B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
100B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
101B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
102B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
103B	tBu	C(O)	CH2	O	-C(O)NMe-CH(F)-C(O)OH
104B	tBu	CHOH	CH2	O	-C(O)NMe-CH(F)-C(O)OH
105B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(F)-C(O)OH
106B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
107B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
108B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
109B	tBu	C(O)	CH2	O	-C(O)NMe-CH(CF_3)-C(O)OH
110B	tBu	CHOH	CH2	O	-C(O)NMe-CH(CF_3)-C(O)OH
111B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(CF_3)-C(O)OH
112B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(CF_3)-C(O)OH
113B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(CF_3)-C(O)OH
114B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(CF_3)-C(O)OH
115B	tBu	C(O)	CH2	O	-C(O)NMe-CH(OH)-C(O)OH
116B	tBu	CHOH	CH2	O	-C(O)NMe-CH(OH)-C(O)OH
117B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(OH)-C(O)OH
118B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
119B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
120B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
121B	tBu	C(O)	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
122B	tBu	CHOH	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
123B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH

124B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
125B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
126B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
127B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
128B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
129B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
130B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
131B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
132B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
133B	tBu	C(O)	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
134B	tBu	CHOH	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
135B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
136B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
137B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
138B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
139B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
140B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
141B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
142B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
143B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
144B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
145B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
146B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
147B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
148B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
149B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
150B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
151B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-

					C(O)OH
152B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
153B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
154B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
155B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
156B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
157B	tBu	C(O)	CH2	O	-C(O)-N(Me)-5-tetrazolyl
158B	tBu	CHOH	CH2	O	-C(O)-N(Me)-5-tetrazolyl
159B	tBu	C(Me)OH	CH2	O	-C(O)-N(Me)-5-tetrazolyl
160B	tBu	C(O)	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl
161B	tBu	CHOH	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl
162B	tBu	C(Me)OH	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl

Among other preferred compounds of the invention are also those represented by the formula:



and pharmaceutically acceptable salts thereof;

wherein;

said compound is selected from a compound code numbered 1C thru 162C, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown

in the row following the compound code number, as set out in the following Table 4 :

Table 4

	R_B	L_3	L_2	L_1	R_C
1C	tBu	C(O)	CH2	CH2	-C(O)NH-CH_2-C(O)OH
2C	tBu	CHOH	CH2	CH2	-C(O)NH-CH_2-C(O)OH
3C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH_2-C(O)OH
4C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH_2-C(O)OH
5C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH_2-C(O)OH
6C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH_2-C(O)OH
7C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
8C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
9C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
10C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
11C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
12C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
13C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
14C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
15C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
16C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
17C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
18C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
19C	tBu	C(O)	CH2	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
20C	tBu	CHOH	CH2	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
21C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
22C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
23C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
24C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-$C(Me)_2$-C(O)OH
25C	tBu	C(O)	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
26C	tBu	CHOH	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
27C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
28C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH

29C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH
30C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH
31C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
32C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
33C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
34C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
35C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
36C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
37C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(CF_3)-C(O)OH
38C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(CF_3)-C(O)OH
39C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(CF_3)-C(O)OH
40C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(CF_3)-C(O)OH
41C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(CF_3)-C(O)OH
42C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(CF_3)-C(O)OH
43C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
44C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
45C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
46C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
47C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
48C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
49C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
50C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
51C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
52C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
53C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
54C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
55C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
56C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
57C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
58C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
59C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH

60C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
61C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
62C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
63C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
64C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
65C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
66C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
67C	tBu	C(O)	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
68C	tBu	CHOH	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
69C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
70C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
71C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
72C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
73C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
74C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
75C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
76C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
77C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
78C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
79C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
80C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
81C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
82C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
83C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
84C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
85C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H
86C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H
87C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H

88C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
89C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
90C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
91C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
92C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
93C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
94C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
95C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
96C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
97C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
98C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
99C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
100C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
101C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
102C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
103C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
104C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
105C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
106C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH
107C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH
108C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH
109C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
110C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
111C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
112C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
113C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
114C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
115C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH

116C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH
117C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH
118C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
119C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
120C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
121C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
122C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
123C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
124C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
125C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
126C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
127C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
128C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
129C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
130C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
131C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
132C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)$_2$-C(O)OH
133C	tBu	C(O)	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
134C	tBu	CHOH	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
135C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
136C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
137C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
138C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
139C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
140C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH

141C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
142C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
143C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
144C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
145C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
146C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
147C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
148C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
149C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
150C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
151C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
152C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
153C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
154C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
155C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
156C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
157C	tBu	C(O)	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl
158C	tBu	CHOH	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl
159C	tBu	C(Me)OH	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl
160C	tBu	C(O)	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl
161C	tBu	CHOH	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl
162C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl

Method of Making the Compounds of the Invention:

Compounds of the invention represented by formula (I) may be prepared by the methods set out below. It will be understood by one skilled in the chemical arts that the reactants

may be varied to analogous molecules to provide desired substitutions in the final reaction product.

Definitions of symbols used in the Schemes:

(PhO)2P(O)N3 – diphenyl phosphorus azide

BBr3 – boron tribromide

BF3-OEt2 – boron trifluoride etherate

BnBr – benzyl bromide

CH3CN – acetonitrile

DMAP - 4-(dimethylamino)pyridine

DMF – N,N-dimethylformamide

DMSO – dimethylsulfoxide

DPPF – dichloro[1,1'-bis(diphenylphosphino)ferrocene

DPPB – 1,4-bis(diphenylphosphino)butane

EDCI – 3-Ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride

Et3N – triethylamine

EtOH – ethanol

H2NCH2CO2Me – methyl glycinate

HN(OMe)Me – N-methyl-O-methyl hydroxylamine

HNMe2 – dimethyl amine

K2CO3 – potassium carbonate

KOH – potassium hydroxide

LAH – lithium aluminum hydride

LiHMDS – lithium hexamethyldisilazide

mCPBA – meta-chloroperbenzoic acid

MeI – methyl iodide

MeOH – methanol

NaBH4 – sodium borohydride

NaH – sodium hydride

NaI – sodium iodide

NMP - N-methylpyrrolidin-2-one

Na-S-R3 – sodium alkylmercaptide

PBr3 – phosphorus tribromide

Pd(OAc)2 – palladium (II) acetate
Pd-C – palladium on carbon
pTSA – para-toluenesulfonic acid
Pyr - pyridine
R2MgBr – alkyl magnesium bromide
R3MgBr – alkyl magnesium bromide
R5MgBr – alkyl magnesium bromide
R2S(O)2NH2 – alkylsulfonamide
tBuC(O)CH2Br – 2-bromopinacolone
Tf2O – triflic anhydride
TFA – trifluoroacetic acid
THF – tetrahydrofuran

Description of the Schemes:

Preparation of diphenyl acid and diphenyl acylaminotetrazole (Scheme 1).

A mixture of 3-substituted-4-hydroxy benzoic acid 1a and methanol is treated with HCl (gas) to yield methyl benzoate ester 1. Methyl benzoate ester 1 is reacted with excess alkyl magnesium bromide to produce tertiary alcohol 2. Tertiary alcohol 2 is converted to phenol 4 by reaction with O-benzyl-2-substituted phenol 3a and BF3-Et2O. O-benzyl-2-substituted phenol 3a is derived from the reaction of 2-substituted phenol 3 with benzylbromide and NaH. Phenol 4 is reacted with triflic anhydride/pyridine to give triflate 5 which is subjected to methoxycarbonylation with Pd(OAc)2, DPPF, CO (689-6895 KPa), methanol and triethylamine in either DMF or DMSO at 80-100 °C to yield methyl ester 6. DPPB may be used instead of DPPF for the methoxycarbonylation reaction. Methyl ester 6 is subjected to palladium catalyzed hydrogenolysis and alkylated with NaH/pinacolone bromide to give ketone 7. Ketone 7 is sequentially reacted with sodium borohydride/MeOH and potassium hydroxide/EtOH/H2O/ 80 °C to produce acid 8. Acid 8 is coupled with EDCI, DMAP and 5-aminotetrazole to give acylamino tetrazole 9. Acid 8 is also coupled with EDCI, DMAP and alkylsulfonamide to give acylsulfonamide 9a.

Preparation of functionalized sidechain analogs (Scheme 2).

Ester 6 is reduced with LAH to give benzyl alcohol 10. Benzyl alcohol 10 is converted to benzylic bromide 11 with PBr3 and alklylated with the enolate of pinacolone to afford ketone 12. Ketone 12 is transformed into keto-ester 14 via Pd-C catalyzed hydrogenolysis, triflate formation with triflic anhydride/pyridine and palladium catalyzed methoxycarbonylation. Keto-ester 14 is subjected to sodium borohydride reduction and potassium hydroxide hydrolysis to produce alcohol-acid 15. Alcohol-acid 15 is coupled with EDCI/Et3N/DMAP/R4NHCH2CO2Me and hydrolyzed with LiOH/EtOH/H2O to afford amide-acid 15a.

Preparation of alkylated pinacolol sidechain (Scheme 3).
Ketone 7 is alkylated with LiHMDS/MeI and reduced with NaBH4/MeOH to give alcohol 16. Alcohol 16 is hydrolyzed with potassium hydroxide to afford alcohol-acid 17. Alcohol-acid 17 is reacted sequentially with 1) EDCI/Et3N/DMAP/R4NHCH2CO2Me; and 2) LiOH/EtOH/H2O to give amide-acid 17a.

Preparation of alkylsulfonylmethyl sidechain analogs (Scheme 4).
Benzylic bromide 11 is reacted with sodium alkylmercaptide and oxidized with mCPBA to give sulfone 18. Sulfone 18 is hydrogenolyzed with Pd-C/H2 and alkylated with pinacolone chloride, potassium carbonate and sodium iodide to produce ketone sulfone 19. Ketone sulfone 19 is reduced with sodium borohydride to afford alcohol sulfone 20.

Preparation of unsymmetrical central link diphenyl scaffold (Scheme 5).
3-Substituted-4-hydroxybenzoic acid is coupled with EDCI/N-methy-N-methoxyamine/DMAP and alkylated with benzyl bromide to give amide 21. Amide 21 is sequentially reacted with R2MgBr and R3MgBr Grignard reagents to afford tertiary alcohol 23. Alcohol 23 is reacted with 2-substituted phenol 3 and BF3-OEt2 to produce diphenylalkane 24. Diphenylalkane 24 is reacted with triflic anhydride/pyridine and methoxycarbonylated with Pd(OAc)2, (DPPF or DPPB), carbon monoxide, MeOH, and Et3N to give ester 26. Ester 26 is hydrogenolyzed with Pd-C/H2 and alkylated with pinacolone bromide to yield ketone ester 27. Ketone ester 27 is reduced with sodium borohydride and hydrolyzed with potassium hydroxide to afford alcohol-acid 28.

Alcohol-acid 28 is coupled with EDCI/Et3N/DMAP/R4NHCH2CO2Me and hydrolyzed with LiOH/EtOH/H2O to afford amide-acid 28a.

Preparation of tertiary alcohol sidechain analog (Scheme 6).

Phenol 4 is alkylated with pinacolone bromide and reacted with MeMgBr or EtMgBr to give alcohol 29. Alcohol 29 is hydrogenolyzed with Pd-C/H2, reacted with triflic anhydride/pyridine and methoxycarbonylated to afford ester 30. Ester 30 is hydrolyzed with potassium hydroxide, coupled with EDCI/Et3N/DMAP/R4NHCH2CO2Me, and hydrolyzed to produce tertiary alcohol amide-acid 31.

Preparation of direct linked tetrazole (Scheme 7).

Acid 8 is reacted with formamide and sodium methoxide to give primary amide 32. Primary amide 32 is treated with trifluoroacetic acid and methylene chloride followed by 2-chloro-1,3-dimethyl-2-imidazolinium hexafluorophosphate to give nitrile 33. Nitrile 33 is reacted with sodium azide and triethylammonium hydrochloride in N-methylpyrrolidin-2-one to afford tetrazole 34.

Preparation of amide (Scheme 8).

Acid 8 is reacted with diphenyl phosphorus azide and triethylamine followed by treatment with dimethylamine and 4-(dimethylamino)pyridine to yield amide 35.

Preparation of esters (Scheme 9).

Acid 8 is treated with sodium iodide and N,N-dimethyl-2-chloroacetamide to give ester 36. Acid 8 is treated with sodium iodide and N-morpholinocarbonylmethyl chloride to give ester 37.

Alternative Synthesis of Diphenylalkyl Scaffold (Scheme 10).

Phenol 2 is heated with pTSA to give olefin 38. Olefin 38 is alkylated with 2-chloropinacolone and reacted with a 2-substituted phenol/BF3-OEt2 to yield phenol 40. Phenol 40 is converted to the corresponding phenolic triflate and reduced to alcohol 41. Alcohol 41 is methoxycarbonylated to afford ester 42. Ester 42 is hydrolyzed to produce acid 8.

Synthesis of Pentynol Phenyl alkyl Phenyl Acids (Scheme 11).

Ester 26 is hydrogenolyzed with Pd-C/H2 and reacted with Tf2O/pyridine to give triflate 43. Triflate 43 is sequentially reacted with 1) TMS-acetylene, PdCl2(PPh3)2, Et3N, and DMF and 2) CsF and water to afford acetylene 44. Acetylene 44 is treated with Zn(OTf)2/t-butyl aldehyde/chiral auxiliary (with or without) to give alcohol 46. Alternatively, acetylene 44 is reacted with LiHMDS/ketone 45 to give alcohol 46. Alcohol 46 is hydrolyzed with KOH/EtOH/H2O to afford acid 47. Acid 47 is sequentially reacted with 1) EDCI/Et3N/DMAP/R4NHCH2CO2Me and 2) LiOH/EtOH/H2O to give amide-acid 48.

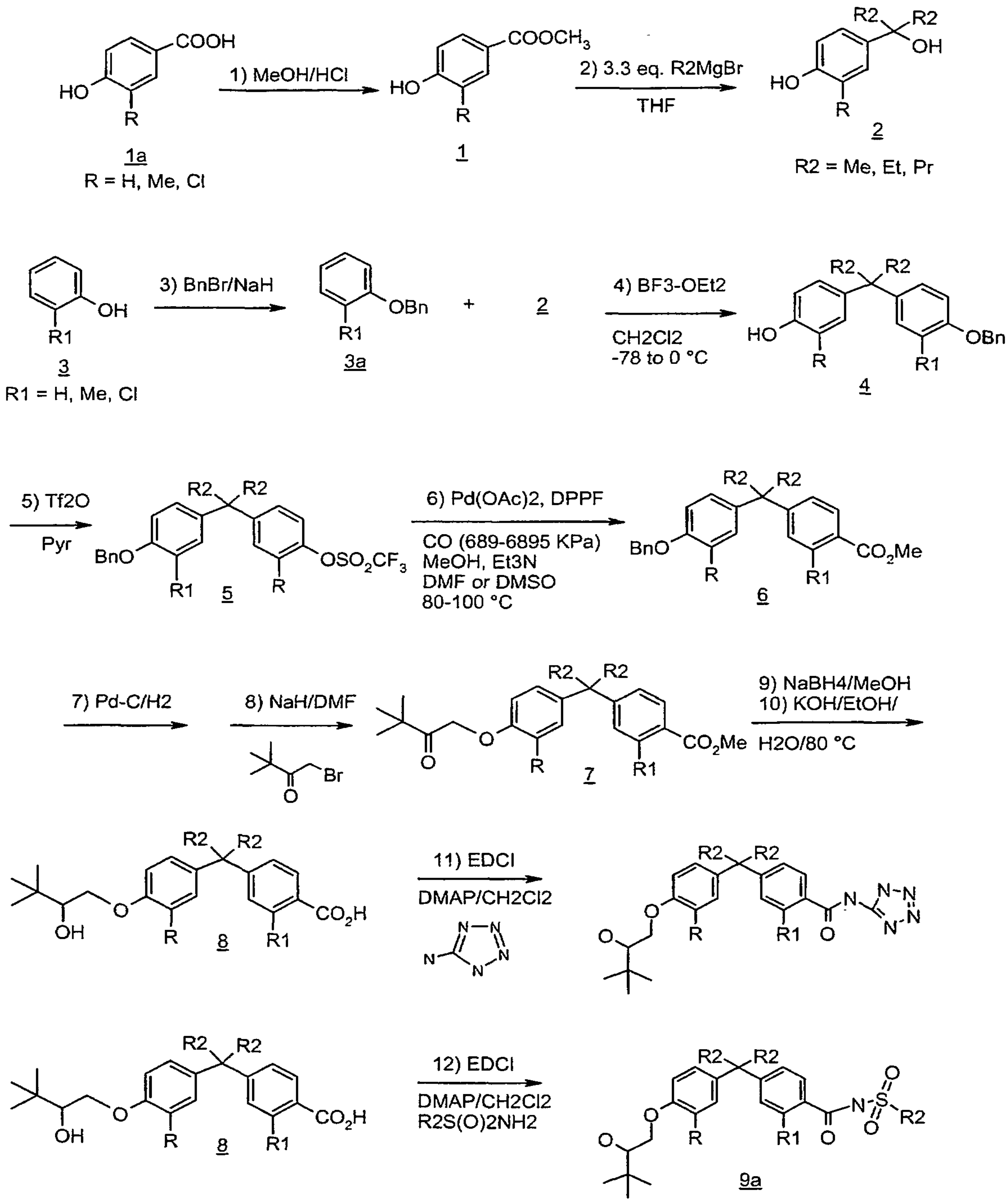
Synthesis of Cis-Pentenol Phenyl alkyl Phenyl Acids (Scheme 12).

Amide-acid 48 is hydrogenated with Lindlar catalyst to afford cis-pentenol amide-acid 49.

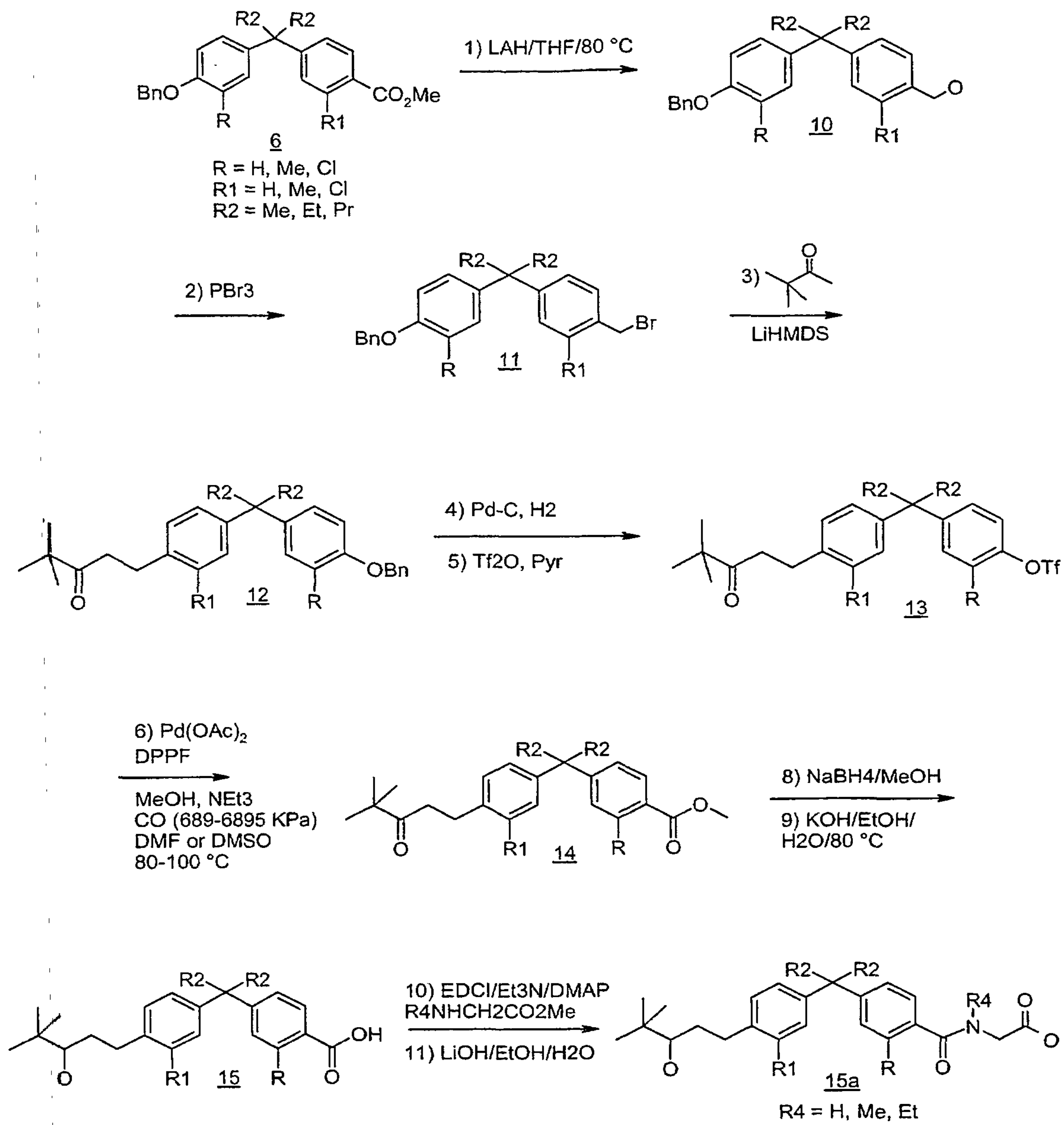
Synthesis of trans-Pentenol Phenyl Alkyl Phenyl Acids (Scheme 13).

Triflate 25 is sequentially reacted with 1) TMS-acetylene, PdCl2(PPh3)2, Et3N, and DMF and 2) CsF and water to afford acetylene 50. Acetylene 50 is treated with Zn(OTf)2/t-butyl aldehyde/chiral auxiliary (with or without) to give alcohol 51. Alternatively, acetylene 50 is reacted with LiHMDS/ketone 45 to give alcohol 51. Alcohol 51 is reduced with LAH or DiBAH to afford trans-pentenol 52. Trans-pentenol 52 is sequentially reacted with 1) Pd-C/H2; 2) Tf2O/pyridine; 3) Pd(OAc)2, DPPF, CO, MeOH, Et3N, DMF; 4) KOH/EtOH/H2O; 5) EDCI/Et3N/DMAP/R4NHCH2CO2Me; and 6) LiOH/EtOH/H2O to give trans-pentenol amide-acid 53. For reaction step 3, DPPB and DMSO.

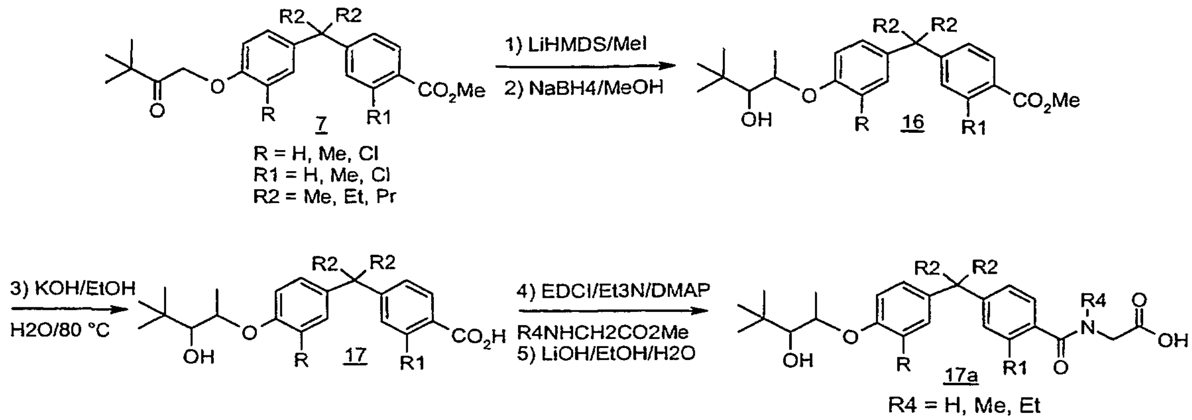
Scheme 1: Synthesis of Diphenyl Scaffold



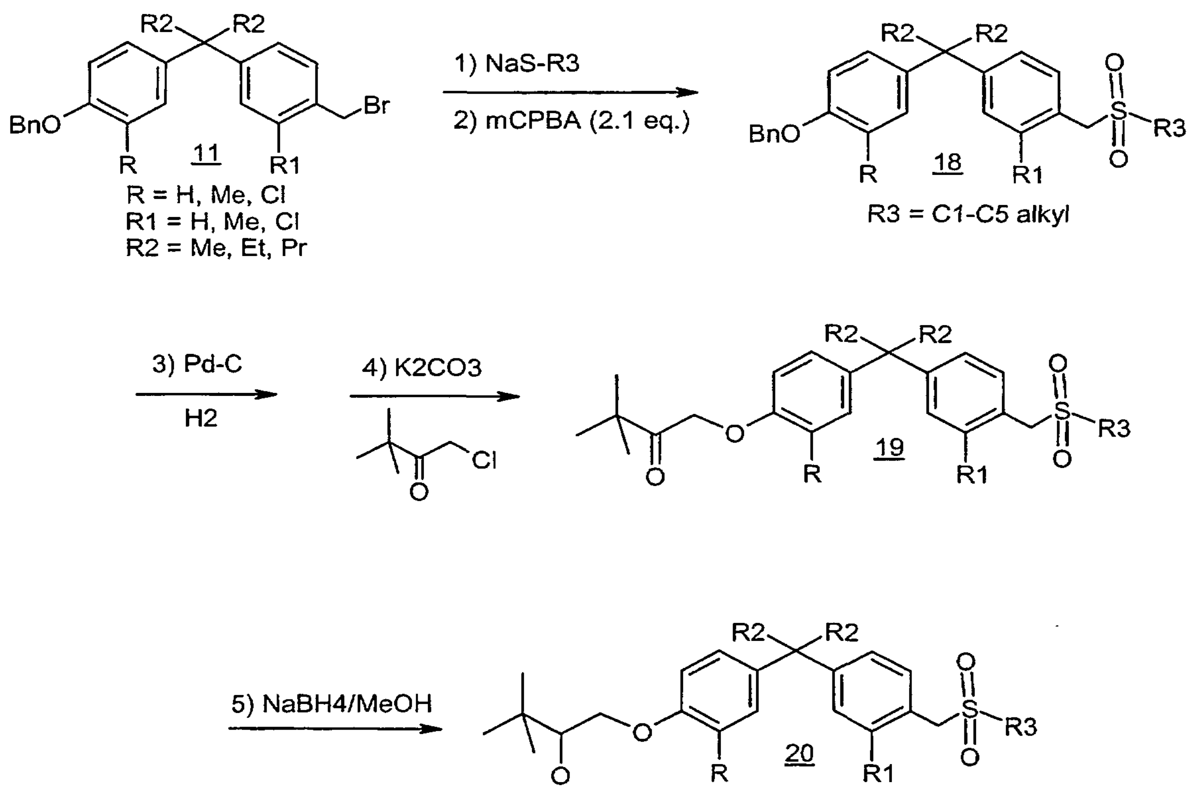
Scheme 2: Synthesis of Functionalized of Sidechain Analogs


R2
R2
BnO
CO2Me
R
R1
6
R = H, Me, Cl
R1 = H, Me, Cl
R2 = Me, Et, Pr
1) LAH/THF/80 °C
10
2) PBr3
Br
11
3)
LiHMDS
OBn
12
4) Pd-C, H2
5) Tf2O, Pyr
OTf
13
6) Pd(OAc)2
DPPF
MeOH, NEt3
CO (689-6895 KPa)
DMF or DMSO
80-100 °C
14
8) NaBH4/MeOH
9) KOH/EtOH/
H2O/80 °C
OH
15
10) EDCI/Et3N/DMAP
R4NHCH2CO2Me
11) LiOH/EtOH/H2O
R4
N
15a
R4 = H, Me, Et

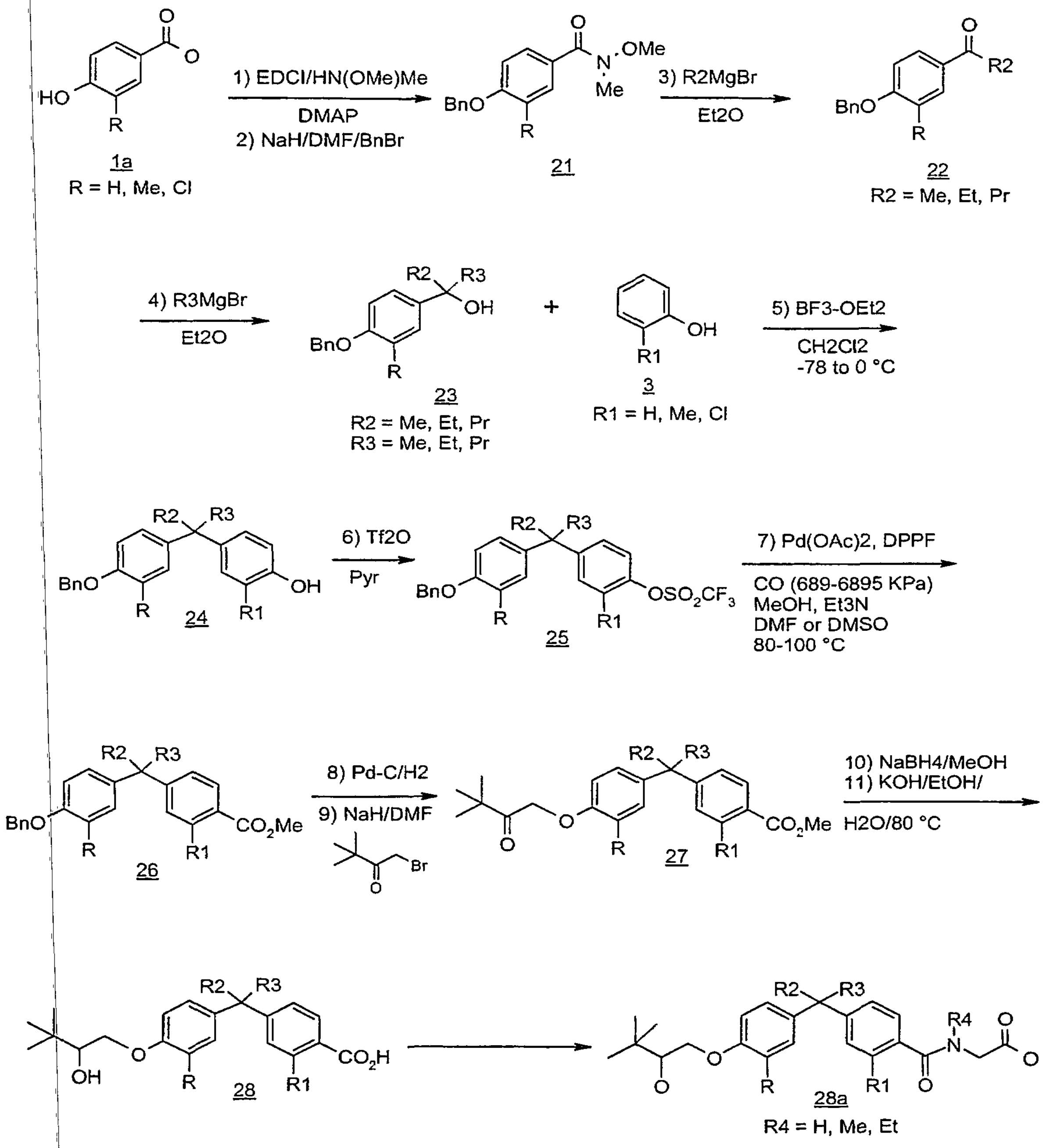
Scheme 3: Synthesis of Alkyl Pinacolol Sidechain



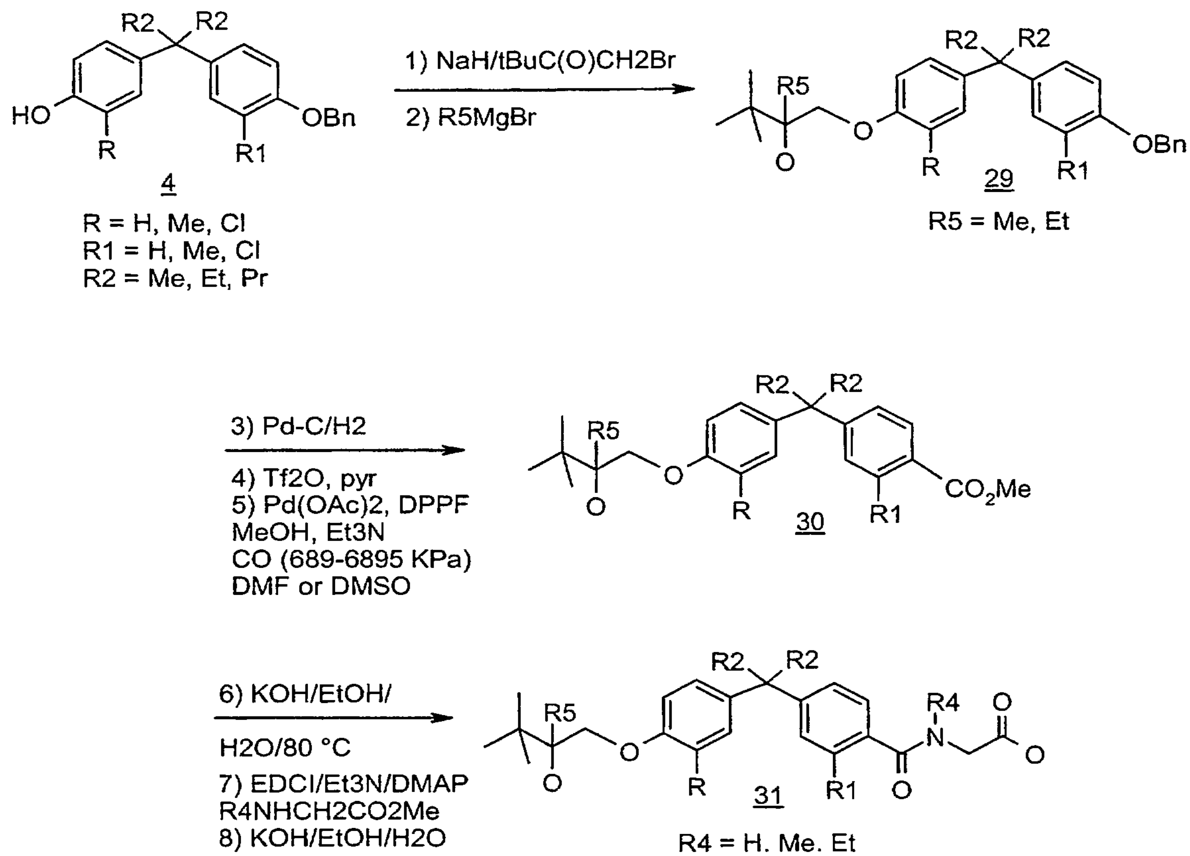
Scheme 4: Synthesis of Alkylsulfonylmethyl Sidechain Analogs



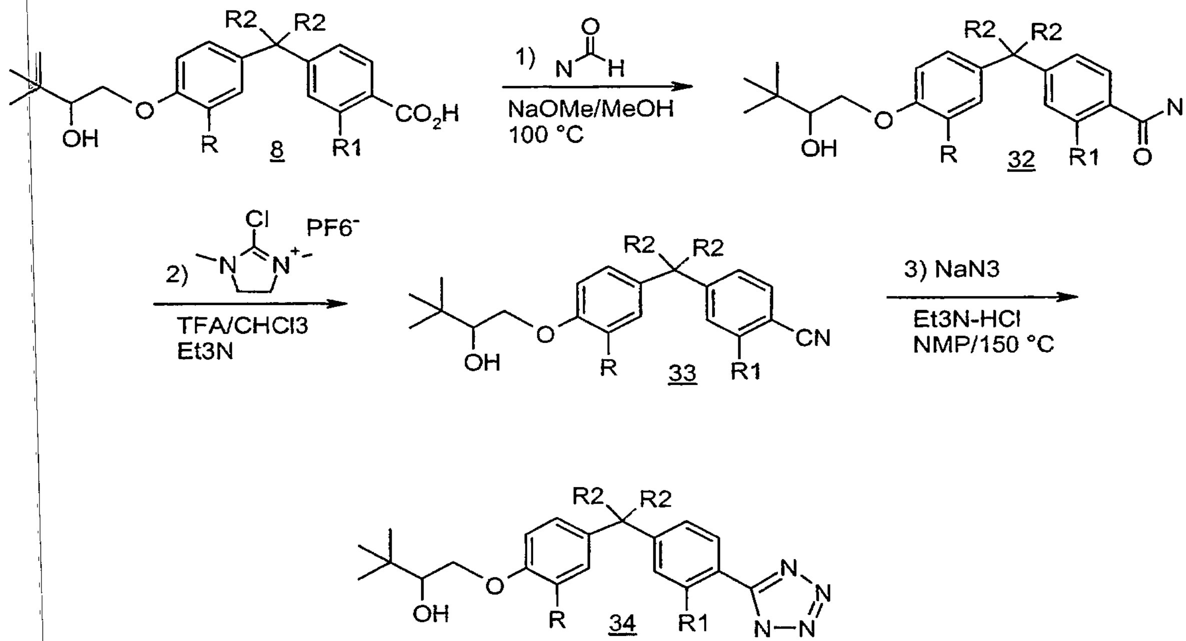
Scheme 5: Synthesis of Unsymmetrical Central Link Diphenyl Scaffold



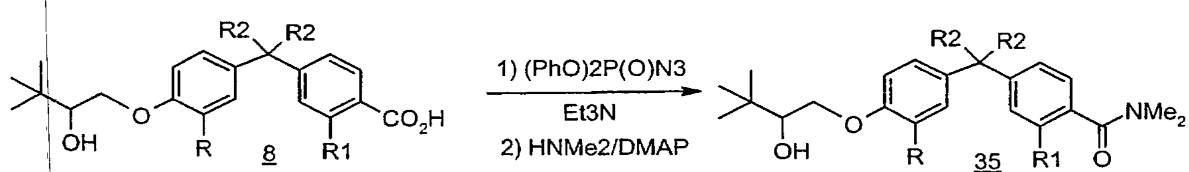
Scheme 6: Synthesis of Tertiary Alcohol Sidechain



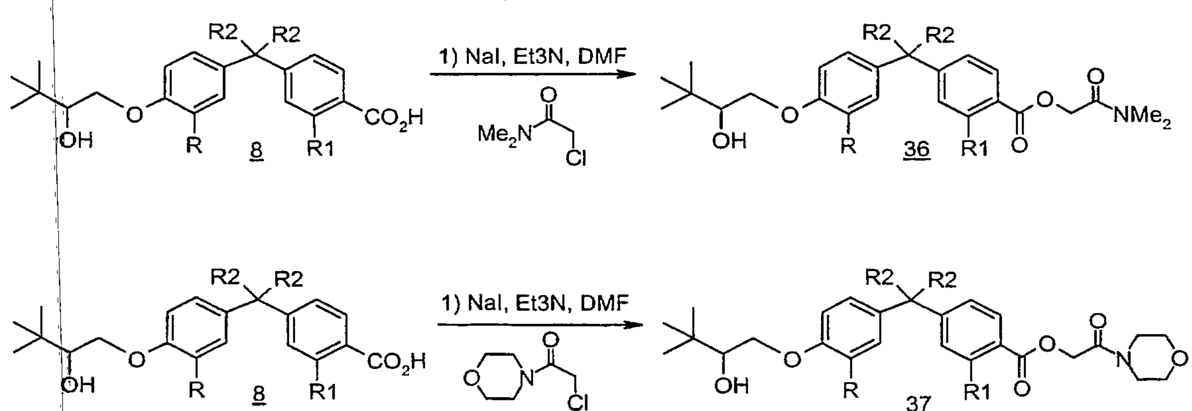
Scheme 7: Synthesis of Direct Linked Tetrazole



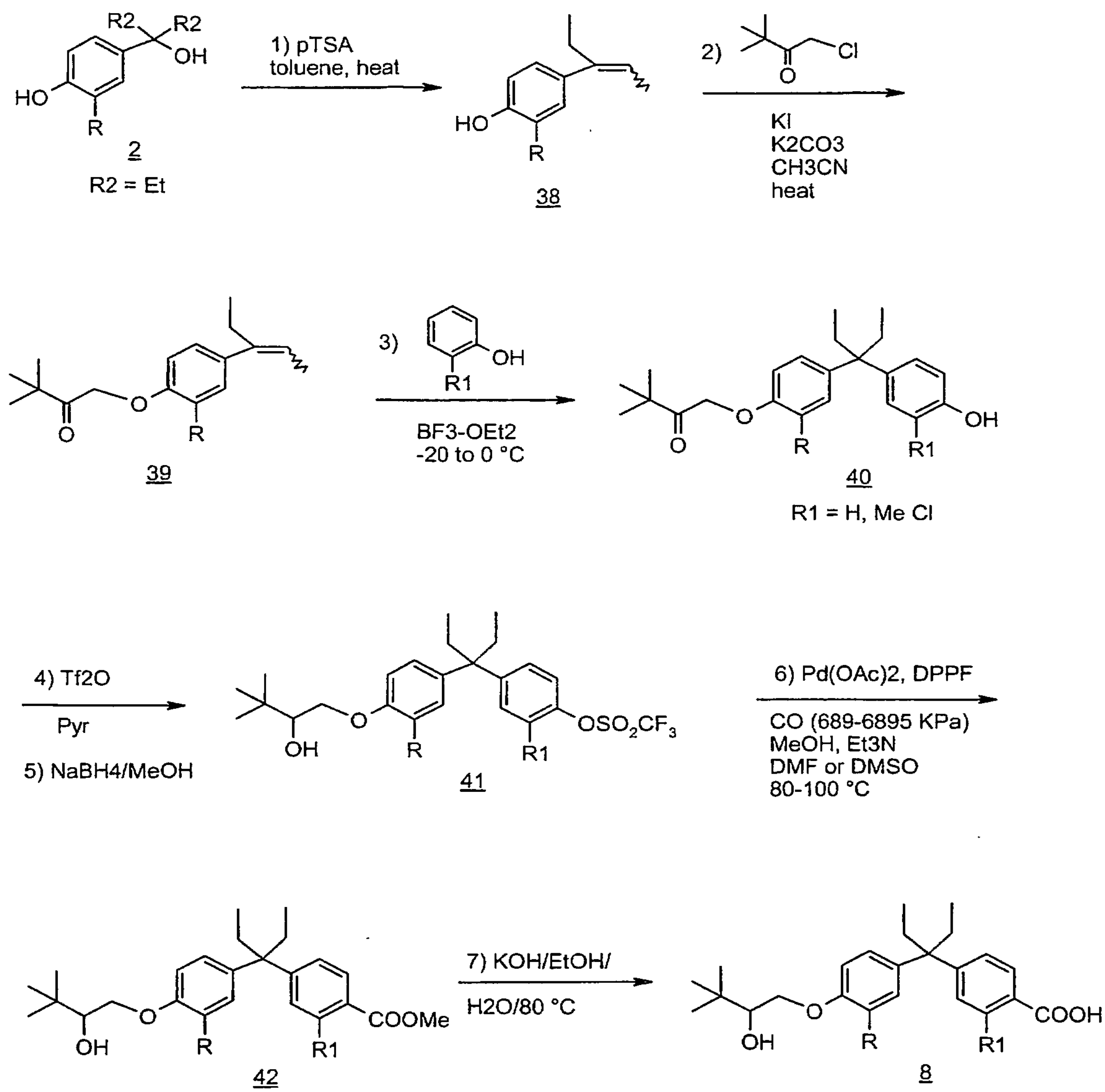
Scheme 8: Synthesis of Amide



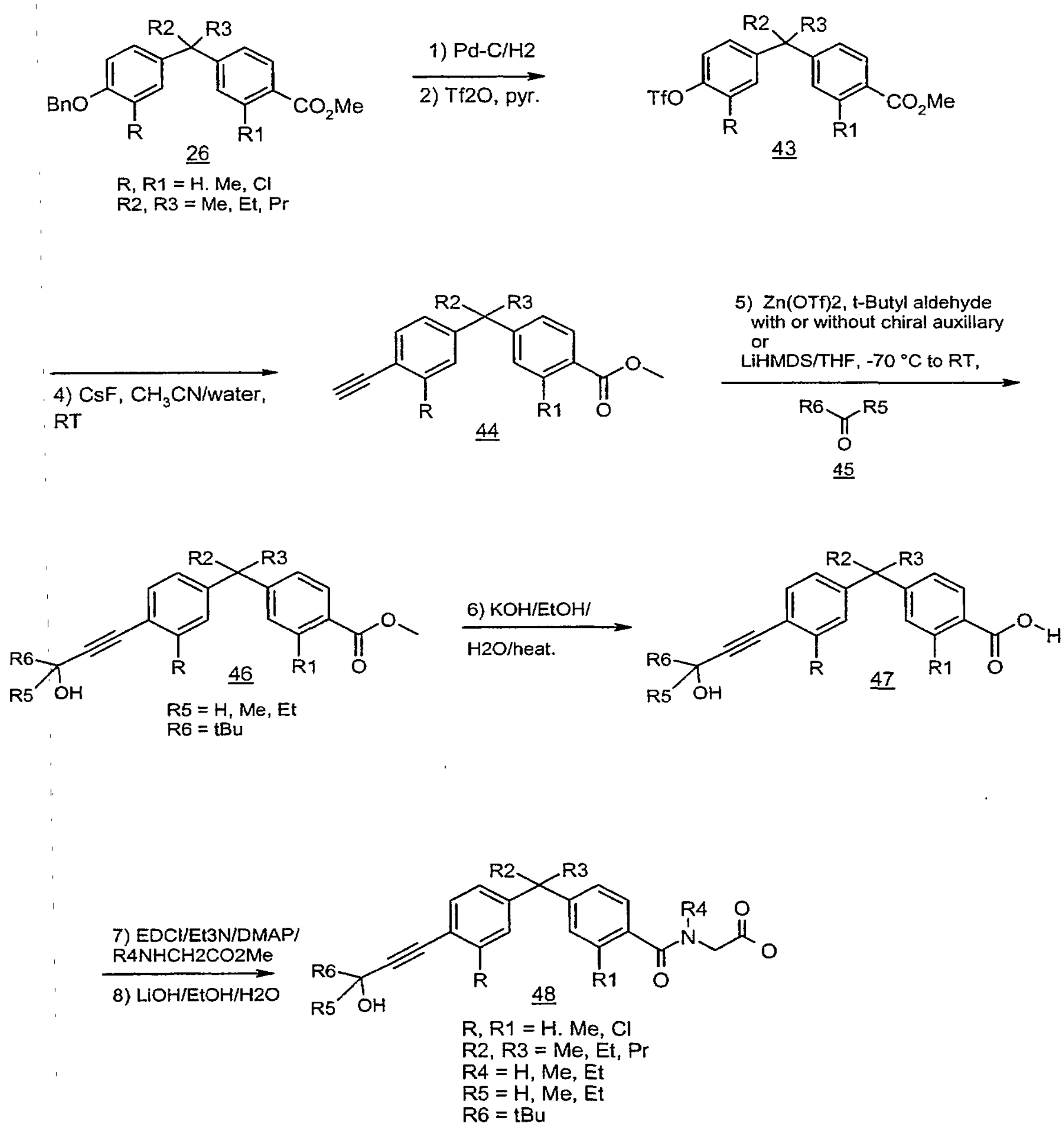
Scheme 9: Synthesis of Ester Prodrugs



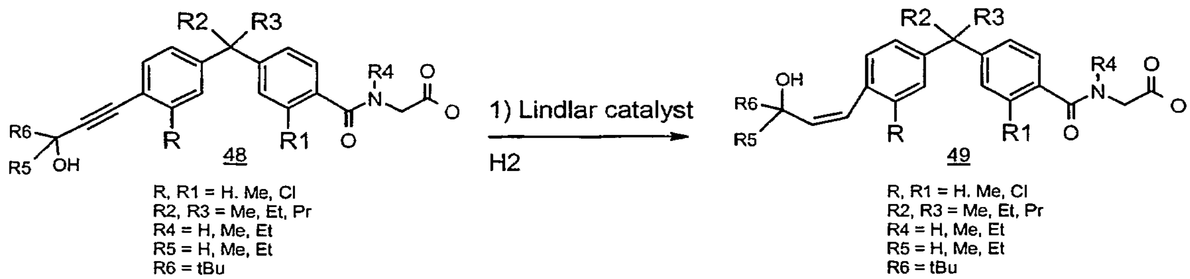
Scheme 10: Alternative Synthesis of Diphenyl Alkyl Scaffold



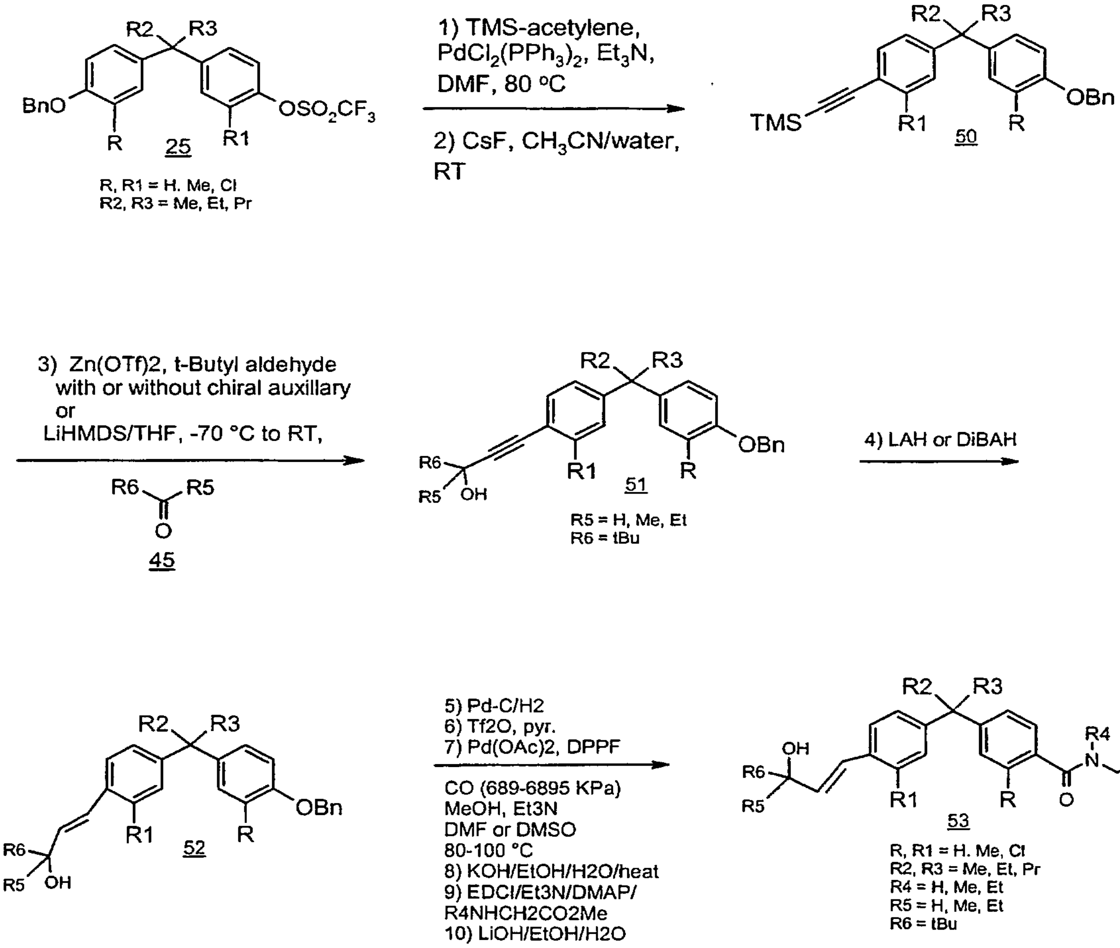
Scheme 11: Synthesis of Pentynol Phenyl Alkyl Phenyl Acids



Scheme 12: Synthesis of Cis-Pentenol Phenyl Alkyl Phenyl Amide-Acids



Scheme 13: Synthesis of Trans-Pentenol Phenyl Alkyl Phenyl Amide-Acids



EXAMPLES

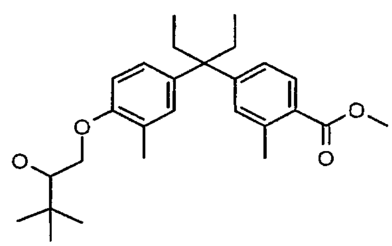
Abbreviations:

The following examples use several standard abbreviations, for example; "RT" is room temperature, "Rt" or t_{ret} are symbols for retention time, and "Hex" refers to hexanes

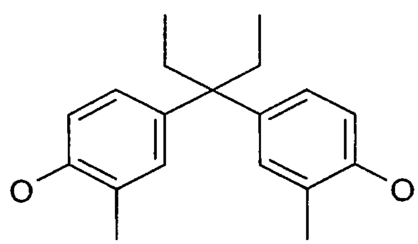
Concentration is performed by evaporation from RT to about 70°C under vacuum (1-10mm)

Example 1

Preparation of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.



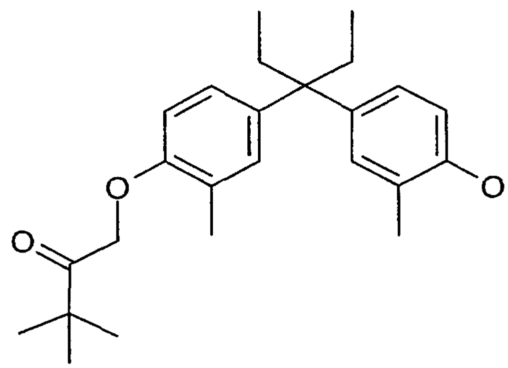
A. 3',3'-Bis[4-hydroxy-3-methylphenyl]pentane.



To a mixture of o-cresol (196 g, 1.81 mol) and 3-pentanone (60 ml, 0.57 mol) is added methanesulfonic acid (45 ml, 0.69 mol) and stirred for 3 days. The reaction is basified to pH 8 with satd Na_2CO_3 and extracted with EtOAc. The organic layer is washed with water (6 X 500 ml), Na_2SO_4 dried, concentrated, chromatographed (2 kg SiO2, Hex to 80% EtOAc/Hex), and triturated with Hex to give the title compound as a white solid (100 g, 61%).

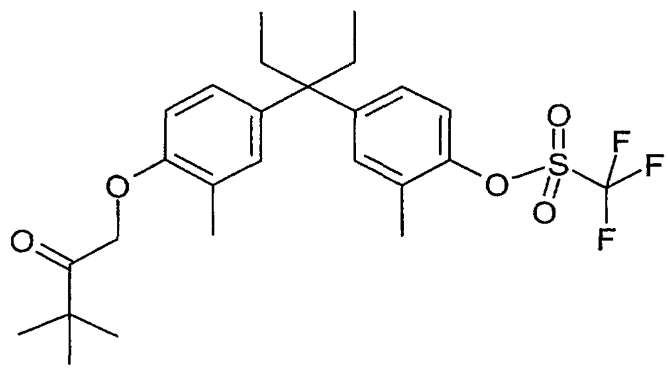
NMR 400 mHz(DMSO): δ 0.49 (t, J = 7.3 Hz, 6H), 1.91 (q, J = 7.3 Hz, 4H), 2.02 (s, 6H), 6.61 (d, J = 8.3 Hz, 2H), 6.73 (d, J = 8.3 Hz, 2H), 6.76 (s, 2H), 8.94 (s, 2H).
High Res. EI-MS: 284.1794; calc. for $C_{19}H_{24}O_2$: 284.1776

B. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl)]-3'-[4-hydroxy-3-methylphenyl]pentane.



To a mixture of 60% NaH disp (8.0 g, 200 mmol) and DMF (600 ml) is added 3,3-bis[4-hydroxy-3-methylphenyl]pentane (56.88 g, 200 mmol) and stirred for 2 h. To the reaction is added 3,3-dimethyl-1-bromo-2-butanone (26.93 ml, 200 mmol) dropwise and stirred overnight. The solvent is removed in-vacuo. To the resulting residue is added EtOAc/water (800 ml/200 ml), acidified to pH 3 with 5N HCl, and partitioned. The organic layer is washed with water (2X), brine, Na_2SO_4 dried, concentrated, and chromatographed (3 kg SiO_2, hex to 15% EtOAc/hex) to give the title compound as a white solid (35 g, 46%).
NMR (300mHz, DMSO): δ 0.52 (t, J = 7.3 Hz, 6H), 1.16 (s, 9H), 1.95 (q, J = 7.3 Hz, 4H), 2.04 (s, 3H), 2.12 (s, 3H), 5.05 (s, 2H), 6.57 (d, J = 9.1 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.81 (m, 2H), 8.97 (s, 1H).
ES-MS: 400(M+NH4).

C. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane

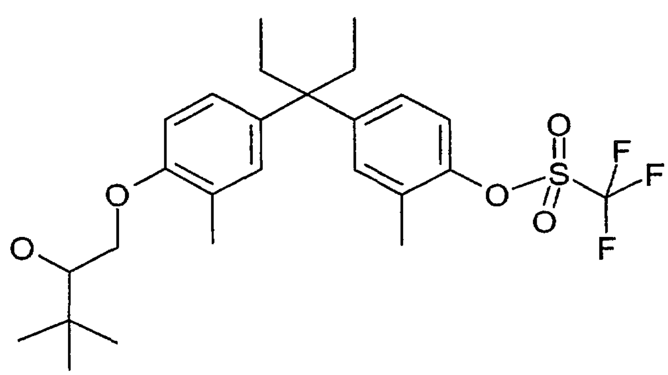


To a 0 °C solution of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl)]-3'-[4-hydroxy-3-methylphenyl]pentane(20 g, 52 mmol), pyridine (30 ml) is added Tf_2O (9.7 ml, 57 mmol). The mixture is warmed to RT and stirred 14 h. The reaction is concentrated. The residue is partitioned between Et_2O/1N HCl. The organic layer is washed with water, brine, Na_2SO_4 dried, concentrated, and chromatographed (hex to 10% EtOAc/hex) to give the title compound as an oil (26.3 g, 98%).

NMR (300mHz, DMSO): δ 0.53 (t, J = 7.3 Hz, 6H), 1.16 (s, 9H), 2.04 (q, J = 7.3 Hz, 4H), 2.14 (s, 3H), 2.28 (s, 3H), 5.07 (s, 2H), 6.61 (d, J = 8.8 Hz, 1H), 6.86 (dd, J = 2.2, 8.8 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 7.10 (dd, J = 2.2, 8.8 Hz, 1H), 7.25 (m, 2H).

ES-MS: 532.5 (M+NH4).

D. 3'-[4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane.



To a 0 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane (25.5 g, 49.5 mmol) and MeOH (200 ml) is added $NaBH_4$ (2.63 g, 59.4 mol) in portions. After stirring for 15 m, the reaction is allowed to warm to RT and stirred for 16 h. The reaction is concentrated and partitioned between Et_2O/1N HCl. The organic layer is washed with water, Na_2SO_4 dried, and concentrated to give the title compound as an oil(26.0 g, quant).

NMR (300mHz, DMSO): δ 0.55 (t, J = 7.3 Hz, 6H), 0.92 (s, 9H), 2.04 (q, J = 7.3 Hz, 4H), 2.11 (s, 3H), 2.28 (s, 3H), 3.46 (m, 1H), 3.76 (m, 1H), 4.03 (m, 1H), 4.78 (d, J = 5.5 Hz, 1H), 6.89 (m, 3H), 7.10 (dd, J = 1.8, 8.8 Hz, 1H), 7.23 (m, 2H).

High Res. EI-MS, m/e: 516.2171; calc. for $C_{26}H_{35}F_3O_5S$: 516.2157.

E. 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

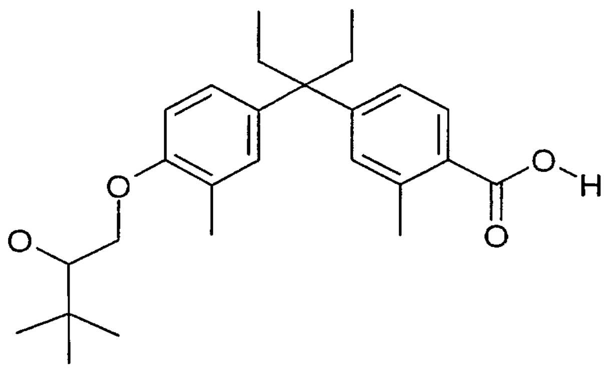
A mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane (27 g, 52.2 mmol), $Pd(OAc)_2$ (1.2 g, 5.22 mmol), Dppf (5.8 g, 10.4 mmol), MeOH (21 ml, 522 mmol), Et_3N (22 ml, 157 mmol), and DMF (100 ml) is pressurized with carbon monoxide (1000 psi) and heated to 110 °C for 48 h. After cooling, the reaction is filtered through diatomaceous earth with EtOAc wash. The filtrate is diluted with 1:1 Et_2O:EtOAc, washed with 1N HCl, and filtered through diatomaceous earth, Na_2SO_4 dried, concentrated, and chromatographed (hex to 10% EtOAc/hex) to give the title compound (14 g, 63%).

NMR 300 MHz(DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 0.92 (s, 9H), 2.04 (q, J = 7.3 Hz, 4H), 2.09 (s, 3H), 2.46 (s, 3H), 3.45 (m, 1H), 3.76 (m, 4H), 4.02 (m, 1H), 4.78 (d, J = 5.5 Hz, 1H), 6.83 (m, 2H), 6.92 (dd, J = 2.2, 8.4 Hz, 1H), 7.07 (m, 2H), 7.74 (d, J = 8.1 Hz, 1H).

High Res. FAB-MS: 426.2750; calc. for $C_{27}H_{38}O_4$: 426.2770.

Example 2

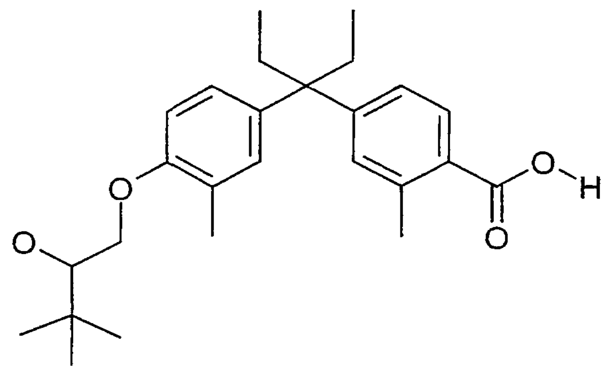
Preparation of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.



A mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane (8.3 g, 19.4 mmol), EtOH (100 ml), water (100 ml) is added KOH (10.8 g, 97 mmol) and heated to 75 °C for 8 h. The reaction is concentrated with a stream of nitrogen and the residue is partitioned between 1:1 Et_2O:EtOAc and 1N HCl. The organic layer is washed with water, Na_2SO_4 dried, concentrated, and chromatographed (gradient 20% EtOAc/$MeCl_2$ to 30% EtOAc/$CHCl_3$) to give the title compound as a white foam (7.85 g, 95%).
NMR mHz(DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 0.92 (s, 9H), 2.05 (q, J = 7.3 Hz, 4H), 2.10 (s, 3H), 2.47 (s, 3H), 3.45 (m, 1H), 3.76 (m, 1H), 4.02 (dd, J = 3.3, 9.9 Hz, 1H), 4.78 (d, J = 5.1 Hz, 1H), 6.83 (m, 2H), 6.92 (dd, J = 1.8, 8.4 Hz, 1H), 7.05 (m, 2H), 7.72 (d, J = 8.1 Hz, 1H), 12.60 (br s, 1H).
High Res. ES-MS: 435.2498; calc. for $C_{26}H_{36}O_4$+Na: 435.2511

Example 3A and Example 3B

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl)]pentane.



A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl)]pentane, Example 3, is chromatographed with a ChiralPak AD column to give enantiomer 1, Example 3A (110 mg, 37%) and enantiomer 2, Example 3B (110 mg, 37%) .

Enantiomer 1, Example 3A
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = 6.2 m
NMR eq. To Example 2.
High Res. ES-MS: 411.2521; calc. for $C_{26}H_{36}O_4$-H: 411.2535

Enantiomer 2, Example 3B
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = 7.3 m
NMR eq. To Example 2.
High Res. ES-MS: 413.2728; calc. for $C_{26}H_{36}O_4$+H: 413.2692

Example 3A Alternate method
Preparation of enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane from enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

Using a procedure analogous to Example 2, enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane, Example 4A, gave the title compound as a glassy solid (1.3 g, quant).

Enantiomer 1, Example 3A
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = 7.0 m
NMR eq. To Example 2.
High Res. ES-MS: 435.2533; calc. for $C_{26}H_{36}O_4$+Na: 435.2511
High Res. ES-MS: 430.2943; calc. for $C_{26}H_{36}O_4$+NH_4: 430.2943
HPLC correlation of Example 3A (derived from chiral HPLC of 2) and 3A (derived from the hydrolysis of 4A):
A mixture of Example 3A (1 mg) (derived from chiral HPLC of 2) and 3A (1 mg)(derived from the hydrolysis of 4A) is dissolved in TFA/20% IPA/80% and analyzed by HPLC; ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); to give a single peak with Rt = 7.0 m.

Example 3B alternate method
Preparation of enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane from enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

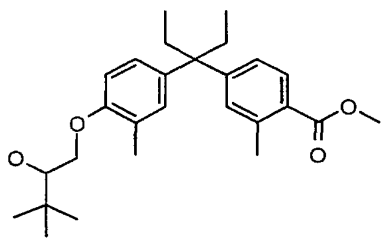
Using a procedure analogous to Example 2, enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane, Example 4B, gave the title compound as a glassy solid (1.3 g, quant).

Enantiomer 2, Example 3B
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = 8.0 m
NMR eq. To Example 2.
High Res. ES-MS: 435.2536; calc. for $C_{26}H_{36}O_4$+Na: 435.2511
HPLC correlation of Example 3B (derived from chiral HPLC of 2) and 3B (derived from the hydrolysis of 4B):

A mixture of Example 3B (1 mg) (derived from chiral HPLC of 2) and 3B (1 mg)(derived from the hydrolysis of 4B) is dissolved in TFA/20% IPA/80% and analyzed by HPLC; ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); to give a single peak with Rt = 8.16 m.

Example 4A and 4B

Preparation of enantiomers of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.



(enantiomer 1)

(enantiomer 2)

A mixture of racemic 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane, Example 1, is chromatographed with a ChiralPak AD column to give enantiomer 1, Example 4A (1.72 g, 49%) and enantiomer 2, Example 4B (1.72 g, 49%) .

Enantiomer 1, Example 4A

HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/80% heptane; 1 ml/m (flow rate); Rt = 5.4 m

NMR eq. To Example 1.

High Res. ES-MS: 444.3130; calc. for $C_{27}H_{38}O_4$+NH_4: 444.3114

Enantiomer 2, Example 4B

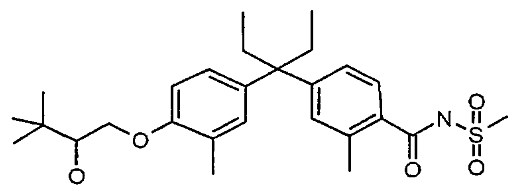
HPLC: ChiralPak AD (4.6X250 mm); 15% IPA/80% heptane; 1 ml/m (flow rate); Rt = 8.0 m

NMR eq. To Example 1.

High Res. ES-MS: 444.3134; calc. for $C_{27}H_{38}O_4$+NH_4: 444.3114

Example 5

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methylsulfonylaminocarbonyl-3-methylphenyl)]pentane.

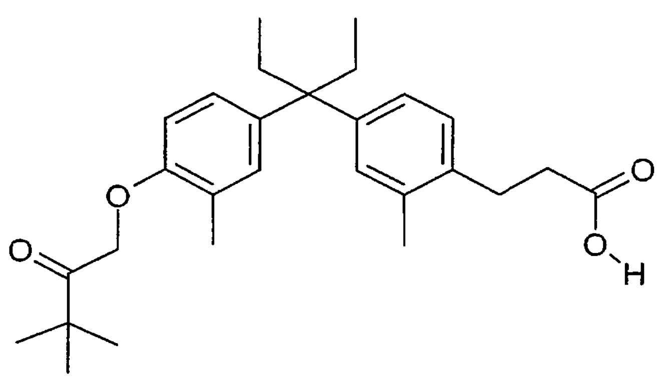


To a mixture of methane sulfonamide (92 mg, 0.97 mmol), EDCI (186 mg, 0.97 mmol), DMAP (118 mg, 0.97 mmol) and CH_2Cl_2 (7 ml) is added 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, Example 1, (400 mg, 0.97 mmol) and stirred overnight. The reaction is diluted with CH_2Cl_2, washed with 1N HCl (4 X 20 ml), Na_2SO_4 dried, concentrated, and chromatographed (gradient $CHCl_3$ to 10% $CH_3CN/CHCl_3$) to give the title compound as a solid (240 mg, 51%). NMR mHz(DMSO): δ 0.60 (t, J = 7.3 Hz, 6H), 1.01 (s, 9H), 2.06 (q, J = 7.3 Hz, 4H), 2.17 (s, 3H), 2.42 (d, J = 2.9 Hz, 1H), 2.49 (s, 3H), 3.43 (s, 3H), 3.70 (d, J = 8.8 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 4.09 (dd, J = 2.4, 9.3 Hz, 1H), 6.71 (d, 8.8 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 2.4, 8.8 Hz, 1H), 7.09 (m, 2H), 7.37 (d, J = 7.8 Hz, 1H), 12.30 (s, 1H).

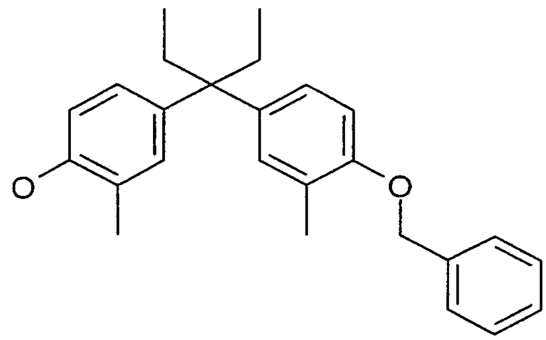
High Res. ES-MS: 490.2633; calc. for $C_{27}H_{39}NO_5S$+H: 490.2627

Example 6

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-carboxylethyl)-3-methylphenyl]pentane.



A. 3'-[4-Benzyloxy-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane.

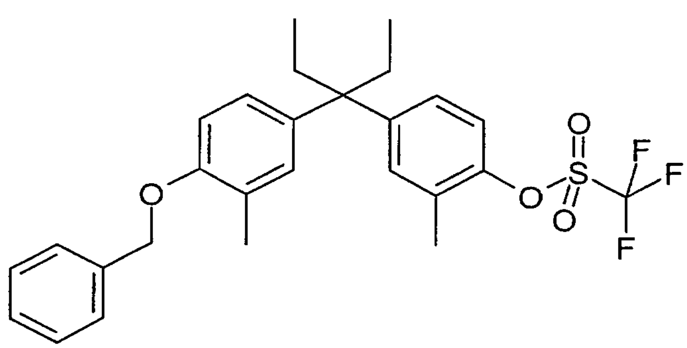


To a solution of 3,3-bis[4-hydroxy-3-methylphenyl]pentane (10 g, 35.2 mmol) and DMF (180 ml) is added 60% NaH disp (1.4 g, 35.2 mmol). After stirring for 30 m, to the reaction is added benzyl bromide (4.2 ml, 35.2 mmol). The mixture is stirred for 14 h and concentrated in vacuo. The residue is partitioned between Et_2O/water. The organic layer is washed with 1N HCl, water, brine, Na_2SO_4 dried, concentrated, and chromatographed ($MeCl_2$) to give the title compound as an oil (6.5 g, 49%).

NMR 300 MHz(DMSO): δ 0.52 (t, J = 7.3 Hz, 6H), 1.96 (q, J = 7.3 Hz, 4H), 2.04 (s, 3H), 2.12 (s, 3H), 5.05 (s, 2H), 6.63 (d, J = 8.1 Hz, 1H), 6.75 (dd, J = 2.2, 8.1 Hz, 1H), 6.79 (s, 1H), 6.89 (m, 3H), 7.44 (m, 5H), 8.96 (s, 1H).

High Res. FAB-MS: 374.2237; calc. for $C_{26}H_{30}O_2$: 374.2246

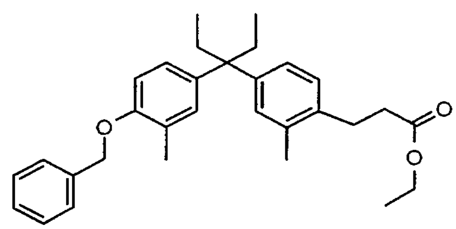
B. 3'-[4-Benzyloxy-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane.



Using a procedure analogous to Example 1C, 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane gives the title compound as an oil (21.5 g, 91%). NMR 300 MHz(DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 2.05 (q, J = 7.3 Hz, 4H), 2.14 (s, 3H), 2.28 (s, 3H), 5.06 (s, 2H), 7.10 (dd, J = 2.2, 8.8 Hz, 1H), 7.26 (m, 2H), 7.34 (d, J = 7.0 Hz, 1H), 7.39 (m, 4H).

High Res. FAB-MS: 506.1743; calc. for $C_{27}H_{29}F_3O_4S$: 506.1739

C. 3'-[4-Benzyloxy-3-methylphenyl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane.

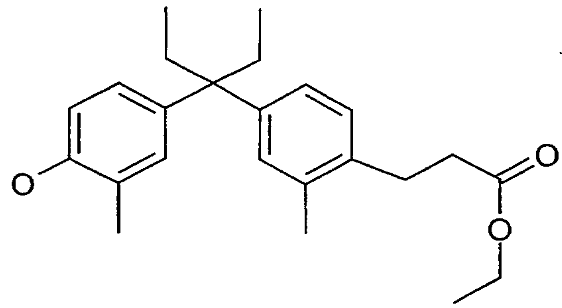


To a mixture of 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane (5.3 g, 10.5 mmol) and THF (5 ml) is sequentially added Pd(dppf)Cl_2 (860 mg, 1.05 mmol), LiCl (1.78 g, 42 mmol), and 0.5 M $BrZnCH_2CH_2CO_2Et$ in THF (63 ml, 31.4 mmol). The mixture is heated to 60 °C for 18 h. After cooling to RT, the mixture is concentrated in-vacuo, partitioned between Et_2O/EtOAc/1N HCl. The organic layer is washed with 1N HCl, water, Na_2SO_4 dried, concentrated, and chromatographed (hex to 10% EtOAc/hex) to give the title compound (2.5 g, 52%).

NMR 400 MHz(DMSO): δ 0.51 (t, J = 7.3 Hz, 6H), 1.14 (t, J = 7.1 Hz, 3H), 2.00 (q, J = 7.3 Hz, 4H), 2.10 (s, 3H), 2.18 (s, 3H), 2.52 (t, J = 8.1 Hz, 2H), 2.75 (t, J = 8.1 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 5.03 (s, 2H), 6.87 (m, 5H), 6.98 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.37 (m, 2H), 7.43 (d, J = 7.1 Hz, 2H).

High Res. ES-MS: 476.3178; calc. for $C_{31}H_{38}O_3$+NH_4: 476.3165

D. 3'-[4-Hydroxy-3-methylphenyl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane

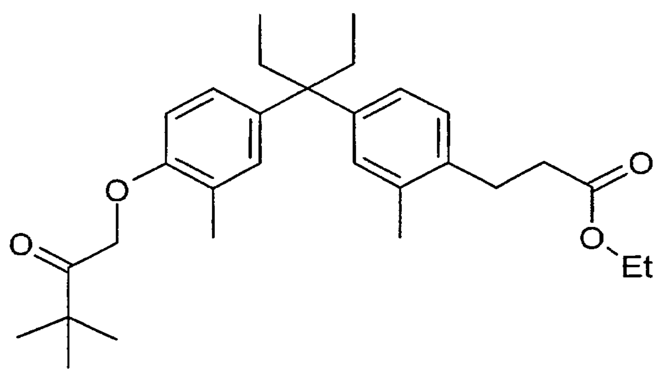


A mixture of 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-(2-ethoxycarbonyl ethyl)-3-methylphenyl]pentane (2.4 g, 5.45 mmol), EtOH (20 ml), and 10% Pd/C (250 mg) is hydrogenated at atmospheric pressure for 18 h. The reaction is filtered through diatomaceous earth with EtOAc wash. The filtrate is concentrated to give the title compound (2 g, quant).

NMR 400 MHz(DMSO): δ 0.49 (t, J = 7.3 Hz, 6H), 1.12 (t, J = 7.1 Hz, 3H), 1.95 (q, J = 7.3 Hz, 4H), 2.01 (s, 3H), 2.18 (s, 3H), 2.52 (t, J = 7.7 Hz, 2H), 2.75 (t, J = 7.7 Hz, 2H), 4.01 (q, J = 7.1 Hz, 2H), 6.61 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.77 (s, 1H), 6.86 (m, 2H), 6.97 (d, J = 7.8 Hz, 1H), 8.98 (s, 1H).

High Res. ES-MS: 391.2218; calc. for $C_{24}H_{32}O_3$+Na: 391.2249

E. 3'-[4-(2-Oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane



Using a procedure analogous to Example 1B, 3'-[4-hydroxy-3-methylphenyl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane and 1-bromo-3,3-dimethyl-2-butanone gave the title compound (2.1 g, 83%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.50 (t, J = 7.3 Hz, 6H), 1.05-1.14 (m, 12H), 1.98 (q , J = 7.3 Hz, 4H), 2.10 (s, 3H), 2.18 (s, 3H), 2.52 (t, J = 7.7, 2H), 2.75 (t, J = 7.7, 2H), 4.02

(q, J = 7.2 Hz, 2H), 5.04 (s, 2H), 6.55 (d, J = 8.3 Hz, 1H), 6.82-6.89 (m, 4H), 6.98 (d, J = 8.1, 1H).

High Res. ES-MS: 489.2990; calc. for $C_{30}H_{42}O_4$+Na: 489.2981

F. 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxylethyl-3-methylphenyl]pentane

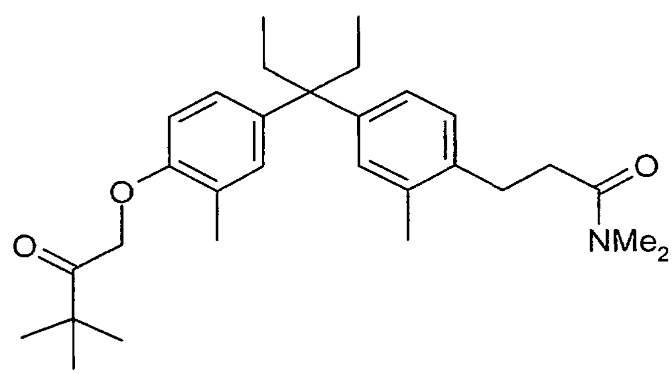
Using a procedure analogous to Example 2, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-ethoxycarbonylethyl)-3-methylphenyl]pentane gives the title compound (1.8 g, 95%).

^{1}H NMR 300 MHz (DMSO-d_6): δ 0.52 (t, J = 7.3 Hz, 6H), 1.16 (s, 9H), 2.01 (q , J = 7.32 Hz, 4H), 2.13 (s, 3H), 2.20 (s, 3H), 2.46 (t, J = 7.3 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 5.06 (s, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.89 (m, 4H), 7.01 (d, J = 7.7 Hz, 1H).

High Res. ES-MS: 461.2669; calc. for $C_{28}H_{38}O_4$+Na: 461.2668

Example 7

Preparation of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-dimethylcarbamoylethyl)-3-methylphenyl]pentane.



To a 0 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-carboxylethyl)-3-methylphenyl]pentane (500 mg, 1.14 mmol), pyridine (101 ul, 1.25 mmol), DMF (4.4 ul, 0.057 mmol) and $MeCl_2$ (4 ml) is added oxalyl chloride (104 ul, 1.2 mmol). After stirring for 10 m, to the mixture is added 2M Me_2NH/THF (2.3 ml, 4.56 mmol). To the reaction is added $MeCl_2$ (4 ml) and stirred at RT for 2 h.

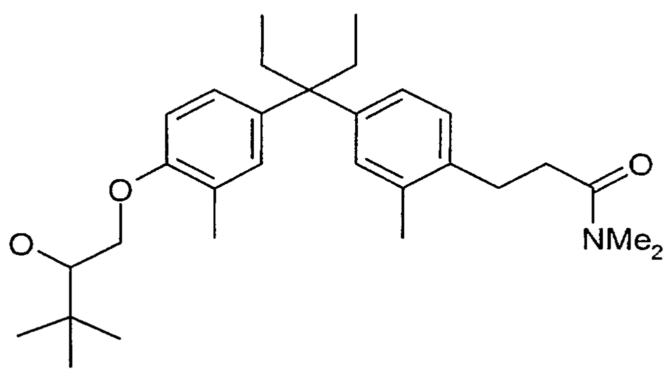
The mixture is concentrated and partitioned between Et_2O/1N HCl. The organic layer is washed with water, Na_2SO_4 dried, concentrated, and chromatographed (hex to CH2Cl2 to 15% EtOAc/$MeCl_2$) to give the title compound as a solid (85 mg, 16%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.51 (t, J = 7.3 Hz, 6H), 1.14 (s, 9H), 1.96 (q , J = 7.3 Hz, 4H), 2.11 (s, 3H), 2.19 (s, 3H), 2.48 (t, J = 7.2, J = 8.8 Hz, 2H, under DMSO peak), 2.69 (t, J = 7.2, J = 8.8 Hz, 2H), 2.79 (s, 3H), 2.88 (s, 3H), 5.05 (s, 2H), 6.55 (d, J = 8.8 Hz, 1H), 6.84-6.87 (m, 4H), 6.99 (d, J = 8.3 Hz, 1H).

ES-MS: 466.2 (M+H)

Example 8

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-dimethylcarbamoylethyl)-3-methylphenyl]pentane.



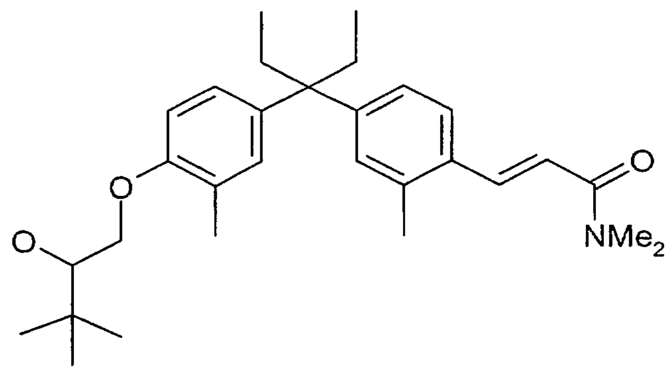
Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-dimethylcarbamoylethyl)-3-methylphenyl]pentane gives the title compound as a white glassy solid (65 mg, quant).

^{1}H NMR 300 MHz (DMSO-d_6): δ 0.53 (t, J = 7.0 Hz, 6H), 0.92 (s, 9H), 6.96 (q , J = 6.96 Hz, 4H), 2.10 (s, 3H), 2.20 (s, 3H), 2.50 (t, J = 6.9, J = 8.4 Hz, 2H, under DMSO peak), 2.71 (t, J = 6.9, J = 8.4 Hz, 2H), 2.80 (s, 3H), 2.90 (s, 3H), 3.45 (m, 1H), 3.75 (m, 1H), 4.01(dd, J = 2.9, J = 6.9 Hz, 1H), 6.80 (d, J = 8.4, 1H), 6.89 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H).

High Res. ES-MS: 490.3301; calc. for $C_{30}H_{45}NO_3$+Na: 490.3297

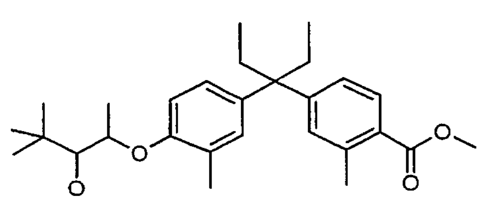
Example 9

Preparation of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-dimethylcarbamoyl-t-ethylidene)-3-methylphenyl]pentane.



To a mixture of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-trifluoromethylsulfonyloxy-3-methylphenyl]pentane (640 mg, 1.24 mmol), $Pd(OAc)_2$ (14 mg, 0.062), DPPP (51 mg, 0.124 mmol), and DMF (2.5 ml) is added Et_3N (0.69 ml, 4.96 mmol). The mixture is purged with N_2 and N,N-dimethylacrylamide (0.39 ml, 3.71 mmol) is added. The reaction is heated to 80 °C for 14 h and then cooled. The mixture is partitioned between EtOAc/water. The organic layer is washed with 1N HCl, water, brine, Na_2SO_4 dried, concentrated, and chromatographed ($MeCl_2$ to 60% EtOAc/$MeCl_2$) to give the title compound as a white foam (90 mg, 16%).
^{1}H NMR 300 MHz (DMSO-d_6): δ 0.55 (t, J = 7.0 Hz, 6H), 0.92 (s, 9H), 2.04 (q, J = 7.0 Hz, 4H), 2.10 (s, 3H), 2.31 (s, 3H), 2.92 (s, 3H), 3.13 (s, 3H), 3.45 (m, 1H), 3.75 (dd, J = 7.4, 9.9 Hz, 1H), 4.02 (dd, J = 3.3, 9.9 Hz, 1H), 4.78 (d, J = 5.1 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.87 (s, 1H), 6.96 (m, 3H), 7.01 (s, 1H), 7.62 (m, 2H).
High Res. ES-MS: 466.3328; calc. for $C_{30}H_{44}NO_3$+H: 466.3321

Preparation of enantiomers of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

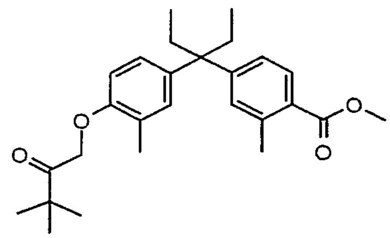


(enantiomer 1) Example 10Da

JB5-A03275-45-1

(enantiomer 2) Example 10Db

A. 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

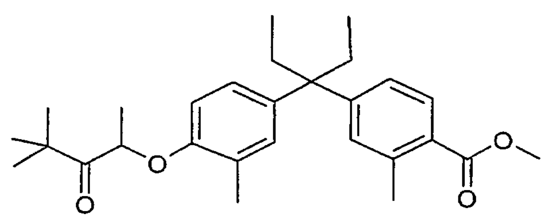


Using a procedure analogous to Example 1B, 3'-[4-hydroxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gave the title compound as a white solid (19.5 g, 88%).

NMR 300 mHz(DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 1.16 (s, 9H), 2.05 (q, J = 7.3 Hz, 4H), 2.13 (s, 3H), 2.47 (s, 3H), 3.79 (s, 3H), 5.07 (s, 2H), 6.59 (d, J = 9.1 Hz, 1H), 6.86 (m, 2H), 7.06 (d, J = 8.1 Hz, 1H), 7.11 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H).

High Res. ES-MS: 442.2953; calc. for $C_{27}H_{36}O_4$+NH_4: 442.2957.

B. 3'-[4-(2-oxo-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

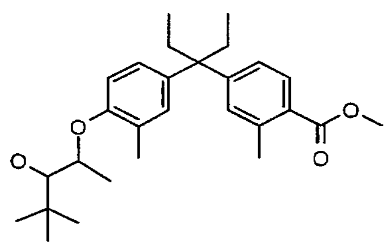


To a –78 °C mixture of 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(2-methoxycarbonyl-3-methylphenyl)]pentane (2.0 g, 4.7 mmol) in THF (10 ml) is added 1M LiHMDS/THF (5.2 ml, 5.2 mmol). The reaction is warmed to –45 °C, stirred for 1.25 h, added MeI (351 ul, 5.6 mmol). After warming to RT and stirred overnight, the reaction is diluted with Et2O, washed with 1N HCl, water, and Na2SO4 dried. The organic solution is concentrated and chromatographed (50% CHCl3/hex) to give the title compound (1.75 g, 85%).

NMR 300 mHz(DMSO): δ 0.53 (t, J = 7.3 Hz, 6H), 1.10 (s, 9H), 1.34 (d, J = 6.6 Hz, 3H), 2.04 (q, J = 7.3 Hz, 4H), 2.10 (s, 3H), 2.46 (s, 3H), 3.79 (s, 3H), 5.32 (q, J = 6.6 Hz, 1H), 6.88 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 7.71 (d, J = 8.1 Hz, 1H).

High Res. ES-MS: 456.3107; calc. for $C_{28}H_{38}O_4$+NH_4: 456.3114

C. 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.



Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gives the title compound (1.6 g, 100%).

NMR 300 mHz(DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), 1.19 (d, J = 5.9 Hz, 3H), 2.07 (m, 7H), 2.48 (s, 3H), 3.08 (dd, J = 1.1, 7.7 Hz, 1H), 3.79 (s, 3H), 4.35 (d, J = 7.7 Hz, 1H), 4.57 (br q, J = 5.9 Hz, 1H), 6.84 (m, 3H), 7.06 (br d, J = 8.4 Hz, 1H), 7.14 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H).

High Res. ES-MS: 456.3107; calc. for $C_{28}H_{38}O_4$+NH_4: 456.3114.

D. Enantiomers of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.

Using a procedure analogous to Example 1D, 3'-[4-(2-oxo-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gave a racemic mixture of the title compound. The mixture is chromatographed (Chiralpak AD) to give enantiomer 1 (543 mg, 36%, Rt =) and enantiomer 2 (822 mg, 55%, Rt =).

Enantiomer 1 Example 10Da

NMR 300 mHz (DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), 1.20 (d, J = 6.2 Hz, 3H), 2.07 (m, 7H), 2.48 (s, 3H), 3.08 (dd, J = 1.5, 7.7 Hz, 1H), 3.79 (s, 3H), 4.35 (d, J = 7.7 Hz, 1H), 4.57 (m, 1H), 6.84 (m, 3H), 7.06 (dd, J = 1.1, 8.4 Hz, 1H), 7.14 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H).

High Res. ES-MS: 458.3257; calc. for $C_{28}H_{40}O_4$+NH_4: 458.3270.

Enantiomer 2 Example 10Db

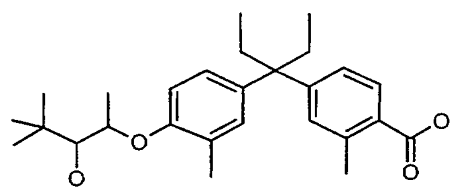
NMR 300 mHz (DMSO): eq. to enantiomer 1.

MS: 440.29 (M+).

High Res. ES-MS: ; calc. for $C_{27}H_{39}NO_5S$+H:

Example 11

Preparation of enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.



(enantiomer 1)

Using a procedure analogous to Example 2, enantiomer 1 of 3'-[4-(1-methyl-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane, Example 10Da, gave the title compound (420 mg, 96%).

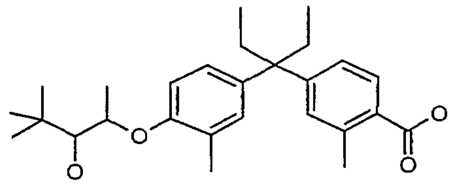
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = m

NMR 300 mHz (DMSO): δ 0.54 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), d, J = 5.9 Hz, 3H), 2.07 (m, 7H), 2.48 (s, 3H), 3.08 (dd, J = 1.1, 7.7 Hz, 1H), 4.35 (d, J = 7.7 Hz, 1H), 4.57 (m, 1H), 6.84 (m, 3H), 7.04 (d, J = 8.1 Hz, 1H), 7.10 (s, 1H), 7.72 (d, J = 8.1 Hz, 1H), 12.60 (br s, 1H).

High Res. ES-MS: 875.5439; calc. for [$C_{27}H_{38}O_4$+Na] + $C_{27}H_{38}O_4$: 875.5438.

Example 12

Preparation of enantiomer 2 of 3'-[4-(2-hydroxy-3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl)]pentane.



(enantiomer 2)

Using a procedure analogous to Example 2, enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane, Example 10Db, gave the title compound (680 mg, 94%).

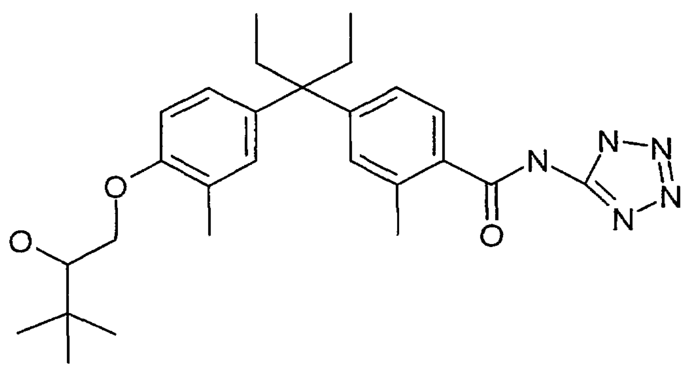
HPLC: ChiralPak AD (4.6X250 mm); 0.1% TFA/20% IPA/80% heptane; 1 ml/m (flow rate); Rt = m

NMR 300 mHz (DMSO): eq. to enantiomer 1.

High Res. ES-MS: 449.2657; calc. for $C_{27}H_{38}O_4$+Na: 449.2668.

Example 12a

Preparation enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



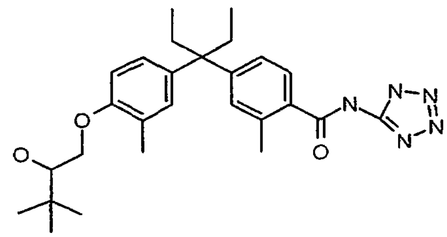
Using a procedure analogous to Example 5, enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, Example 3A, and 5-aminotetrazole give the title compound (440 mg, 95%).

NMR 300 mHz (DMSO): 0.57 (t, J = 7.3 Hz, 6H), 0.92 (s, 9H), 2.09 (m, 7H), 2.40 (s, 3H), 3.46 (m, 1H), 3.76 (dd, J = 7.3, 10.2 Hz, 1H), 4.03 (dd, J = 3.3, 10.2 Hz, 1H), 4.79 (d, J = 5.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.89 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.12 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 12.23 (s, 1H), 16.00 (br s, 1H).

High Res. ES-MS: 480.2983; calc. for $C_{27}H_{37}N_5O_3$+H: 480.2975.

Example 12b

Preparation enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



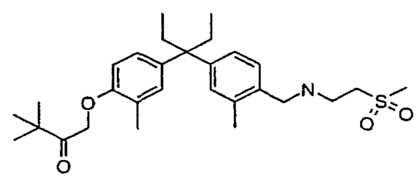
Using a procedure analogous to Example 5, enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, Example 3B, and 5-aminotetrazole gives the title compound (385 mg, 83%).

NMR 300 mHz (DMSO): eq. to enantiomer of 1.

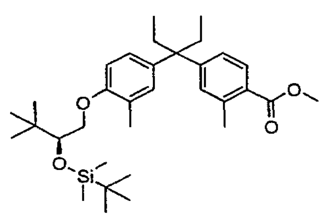
High Res. ES-MS: 480.2968; calc. for $C_{27}H_{37}N_5O_3$+H: 480.2975.

Example 13

Preparation of 1-[4-(1-ethyl-1-{4-[(2-methanesulfonyl-ethylamino)-methyl]-3-methyl-phenyl}-propyl)-2-methyl-phenoxy]-3,3-dimethyl-butan-2-one.



A. Methyl 4-(1-{4-[2-(tert-Butyldimethylsilanyloxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methyl-benzoate.

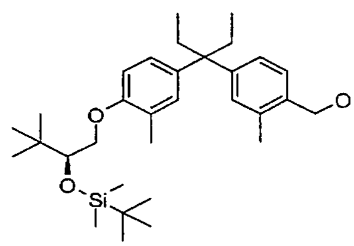


To a solution of the methyl 4-(1-{4-[2-(hydroxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzoate (4.79 g, 11.24 mmol), Example 1, in

DMF (40 mL) is added imidazole (1.14 g, 16.87 mmol) followed by the addition of TBSCl (1.78 g, 11.80 mmol). The mixture is stirred at RT overnight and concentrated. The mixture is partitioned between 0.1 M HCl (100 mL) and EtOAc (100 mL). The aqueous layer is extracted with EtOAC. The combined organic layers is $MgSO_4$ dried, concentrated, and chromatographed (10% EtOAc/Hex) to give the title compound (4.37 g, 72%).

^{1}H NMR ($CDCl_3$): δ 0.04 (s, 3H), 0.10 (s, 3H), 0.60 (t, J = 7.0 Hz, 6H), 0.89 (s, 9H), 0.96 (s, 9H), 2.04-2.09 (m, 4H), 2.16 (s, 3H), 2.55 (s, 3H), 3.66 (dd, J = 5.6, 3.6 Hz, 1H), 3.82-3.86 (m, 4H), 3.97 (dd, J = 10.0, 3.2 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.83-7.06 (m, 4H), 7.79 (d, J = 7.6 Hz, 1H). ES-MS (m/z): calcd for $C_{33}H_{52}O_4Si$ (M^+): 540.9; found: 541.2.

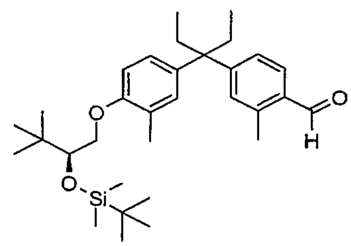
B. [4-(1-{4-[2-(tert-Butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylphenyl]-methanol.



To a 0 °C solution of the methyl 4-(1-{4-[2-(t-butyldimethylsilanyloxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methyl-benzoate (4.37 g, 8.09 mmol) in THF (50 mL) is added $LiAlH_4$ (0.31 g, 8.09 mmol). The reaction is stirred for 10 m and allowed to warm to RT overnight. The mixture is cooled to 0 °C and quenched successively with H_2O (0.3 mL), 15 % NaOH (0.3 mL) and H_2O (0.9 mL). The mixture is stirred for 10 m, warmed to RT, stirred for 20 m, filtered through celite with EtOAc (100 mL) wash, and concentrated to give the title compound (4.14 g, 8.08 mmol, 99%).

^{1}H NMR ($CDCl_3$): δ 0.04 (s, 3H), 0.10 (s, 3H), 0.59 (t, J = 7.1 Hz, 6H), 0.89 (s, 9H), 0.94 (s, 9H), 2.05 (q, J = 7.1 Hz, 4H), 2.17 (s, 3H), 2.31 (s, 3H), 3.66 (dd, J = 6.0, 3.6 Hz, 1H), 3.70 (t, J = 5.6 Hz, 1H), 3.84 (dd, J = 9.8, 5.2 Hz, 1H), 3.97 (dd, J = 9.8, 3.6 Hz, 1H), 4.67 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.88-7.02 (m, 4H), 7.21 (d, J = 8.0 Hz, 1H). ES-MS (m/z): calcd for $C_{32}H_{56}NO_3Si$ $(M+NH_4)^+$: 530.9; found: 530.2.

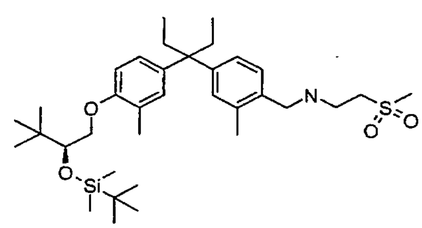
C. 4-(1-{4-[2-(t-Butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzaldehyde.



To a solution of [4-(1-{4-[2-(t-butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylphenyl]methanol (0.25 g, 0.48 mmol) in CH_2Cl_2 (4 mL) is added powdered 4Å molecular sieves (250 mg) followed by the addition of NMO (84 mg, 0.72 mmol), and TPAP (8.4 mg, 0.02 mmol). The resulting mixture is stirred at RT for 5 m, filtered through silica gel, washed with EtOAc, and the combined filtrate is concentrated to give the title compound (0.20 g, 83%).

^{1}H NMR ($CDCl_3$): δ 0.04 (s, 3H), 0.10 (s, 3H), 0.61 (t, J = 7.2 Hz, 6H), 0.89 (s, 9H), 0.96 (s, 9H), 2.09 (q, J = 7.2 Hz, 4H), 2.17 (s, 3H), 2.62 (s, 3H), 3.67 (dd, J = 5.4, 3.4 Hz, 1H), 3.85 (dd, J = 9.8, 5.4 Hz, 1H), 3.97 (dd, J = 9.8, 3.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.84-6.92 (m, 2H), 7.08 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 10.21 (s, 1H). ES-MS (m/z): calcd for $C_{32}H_{51}O_3Si$ $(M+H)^+$: 511.8; found: 511.2.

D. [4-(1-{4-[2-(t-Butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzyl]-(2-methanesulfonylethyl)amine.

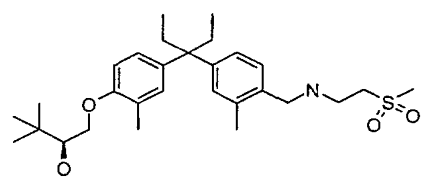


To a mixture of 4-(1-{4-[2-(t-butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzaldehyde (2.40 g, 4.71 mmol), Et_3N (0.9 ml, 6.12 mmol), and 2-aminoethylmethylsulfone hydrochloride (0.78 g, 5.18 mmol) is treated with $Ti(O\textit{i}Pr)_4$ (1.8 ml, 6.12 mmol). The mixture is stirred for 1 h, diluted with CH_3OH (20 mL), then $NaBCNH_3$ (0.33 g, 5.18 mmol) is added. The mixture is stirred overnight, quenched with H_2O (3 mL), stirred for 1 h., and filtered through SiO_2 with EtOAc (100

mL) wash. The filtrate is concentrated and chromatographed (75-80%EtOAc) to give the title compound (1.47 g, 2.38 mmol, 51%).

^{1}H NMR ($CDCl_3$), δ 0.05 (s, 3H), 0.12 (s, 3H), 0.61 (t, J = 7.4 Hz, 6H), 0.91 (s, 9H), 0.97 (s, 9H), 2.05 (q, J = 7.4 Hz, 4H), 2.19 (s, 3H), 2.33 (s, 3H), 2.99 (s, 3H), 3.21-3.27 (m, 3.5 H), 3.66-3.72 (m, 1.5 H), 3.83 (s, 2H), 3.86 (t, J = 5.9 Hz, 1H), 3.98 (dd, J = 9.8, 3.4 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.86-6.88 (m, 1H), 6.92 (dd, J = 8.3, 2.4 Hz, 1H), 6.99 (s, 1H), 7.00 (bs, 1H), 7.14 (d, J = 8.2 Hz, 1H). ES-MS (m/z): calcd for $C_{35}H_{60}O_4SSi$ $(M+H)^+$: 619.0; found: 619.6.

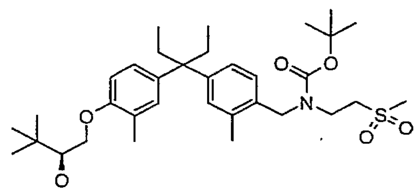
E. 1-[4-(1-Ethyl-1-{4-[(2-methanesulfonylethylamino)methyl]-3-methylphenyl}propyl)-2-methylphenoxy]-3,3-dimethylbutan-2-ol.



To a mixture of [4-(1-{4-[2-(t-butyldimethylsilanyloxy)-3,3-dimethylbutoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzyl]-(2-methanesulfonylethyl)amine (1.47 g, 2.43 mmol) in THF (30 mL) is added 1M TBAF (2.7 mL, 2.7 mmol), and refluxed for 2 h. After cooling to RT, the mixture is diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers are $MgSO_4$ dried, concentrated, and chromatographed (80% EtOAc/Hex) to give the title compound (0.97 g, 1.93 mmol, 79%).

^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.4 Hz, 6H), 1.02 (s, 9H), 2.05 (q, J = 7.4 Hz, 4H), 2.18 (s, 3H), 2.34 (s, 3H), 3.01 (s, 3H), 3.32 (bs, 4H), 3.71 (dd, J = 8.8, 2.4 Hz, 1H), 3.86 (t, J = 9.3 Hz, 1H), 3.88 (s, 2H), 4.09 (dd, J = 9.3, 2.4 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.89 (bs, 1H), 6.90-6.96 (m, 1H), 6.98 (s, 1H), 7.00 (s, 1H), 7.13 (d, J = 7.5 Hz, 1H). ES-MS (m/z): calcd for $C_{29}H_{46}O_4S$ $(M+H)^+$: 504.8; found: 504.4.

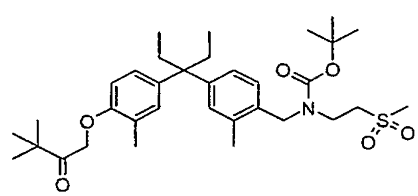
F. t-Butyl (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzyl)-(2-methanesulfonylethyl)carbamate.



To a mixture of of 1-[4-(1-ethyl-1-{4-[(2-methanesulfonylethyl-amino)methyl]-3-methylphenyl}propyl)-2-methylphenoxy]-3,3-dimethylbutan-2-ol (0.97 g, 1.92 mmol), $NaHCO_3$ (0.32 g, 3.84 mmol), H_2O(10 mL), and THF (5 mL), is added $(Boc)_2O$ (0.46 g, 2.11 mmol). The reaction is stirred overnight, diluted with H_2O (10 mL), and extracted with EtOAc (2 x 20 mL). The combined organic layers are washed with 0.1 M HCl (15 mL), brine (10 mL); $MgSO_4$ dried, and chromatographed (40% EtOAc/Hex) to give the title compound (0.86 g, 1.43 mmol, 74%).

^{1}H NMR ($CDCl_3$), δ 0.61 (t, J = 7.3 Hz, 6H), 1.02 (s, 9H), 1.45 (bs, 9H), 2.05 (q, J = 7.3 Hz, 4H), 2.19 (s, 3H), 2.24 (s, 3H), 2.44 (bs, 1H), 2.70-3.20 (b, 5H), 3.58 (bs, 2H), 3.71 (dd, J = 8.8, 2.9 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 8.8, 2.9 Hz, 1H), 4.47 (s, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.80-7.01 (m, 5H). ES-MS (m/z): calcd for $C_{34}H_{57}N_2O_6S$ $(M+NH_4)^+$: 621.9; found: 621.3.

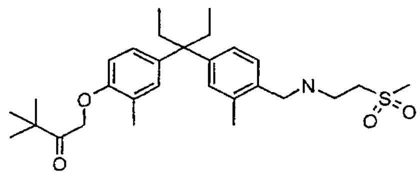
G. t-Butyl (4-{1-[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]-1-ethylpropyl}-2-methylbenzyl)-(2-methanesulfonylethyl)carbamate.



Using a procedure analogous to Example 13C, from t-butyl (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzyl)-(2-methanesulfonylethyl)carbamate (0.26 g, 0.43 mmol) to give the title compound (0.25 g, 0.42 mmol, 95%).

^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.5 Hz, 6H), 1.26 (s, 9H), 1.48 (bs, 9H), 2.05 (q, J = 7.5 Hz, 4H), 2.23 (s, 3H), 2.25 (s, 3H), 2.60-3.20 (m, 5H), 3.57 (bs, 2H), 4.46 (s, 2H), 4.84 (s, 2H), 6.50 (d, J = 8.1 Hz, 1H), 6.80-7.01 (m, 5H). ES-MS (m/z): calcd for $C_{34}H_{51}O_6S$: 601.9; found: 602.2.

H. 1-[4-(1-Ethyl-1-{4-[(2-methanesulfonylethylamino)-methyl]-3-methylphenyl}propyl)-2-methylphenoxy]-3,3-dimethylbutan-2-one.

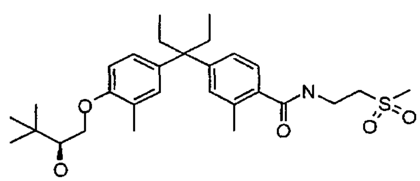


To a mixture of t-butyl (4-{1-[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]-1-ethylpropyl}-2-methylbenzyl)-(2-methanesulfonylethyl)carbamate (0.25, g, 0.41 mmol) and CH_2Cl_2 (5 mL) is added TFA (5 mL,), stirred for 10 m, and concentrated. The residue is diluted with EtOAc (100 mL), washed with sat.d $NaHCO_3$ (2 x 30 mL); $MgSO_4$ dried, and chromatographed (90% EtOAc) to give the title compound (0.19 g, 0.39 mmol, 95%).

^{1}H NMR ($CDCl_3$), δ 0.61 (t, J = 7.2 Hz, 6H), 1.27 (s, 9H), 2.05 (q, J = 7.2 Hz, 4H), 2.25 (s, 3H), 2.32 (s, 3H), 2.99 (s, 3H), 3.25 (s, 4H), 3.81 (s, 2H), 4.84 (s, 2H), 6.49 (d, J = 8.3 Hz, 1H), 6.85-7.00 (m, 4H), 7.13 (d, J = 7.7 Hz, 1H). ES-MS (m/z): calcd for $C_{29}H_{44}NO_4S$ $(M+H)^+$: 502.7; found: 502.2.

Example 14

Preparation of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl] propyl}-N-(2-methanesulfonylethyl)-2-methylbenzamide.



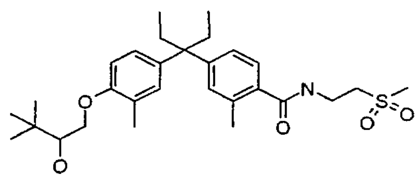
To a mixture of 4-(1-{4-[2-(hydroxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzoic acid, Example 1, (0.53 g, 1.29 mmol), 2-aminoethylmethylsulfone hydrochloride (0.21 g, 1.29 mmol), HOBt (0.19 g, 1.43 mmol), Et_3N (0.72 mL, 5.19 mmol) and CH_2Cl_2 (10 mL) is added EDCI (0.249 g, 1.29 mmol) and stirred overnight. The reaction is diluted with CH_2Cl_2 (50 mL), washed with 1M HCl (2 x 30 mL), H_2O (20 mL), satd $NaHCO_3$ (2 x 20 mL), and brine (20 mL). The organic layer

is $MgSO_4$ dried, concentrated, and chromatographed (75% EtOAc/Hex) to give the title compound (0.51 g, 76%).

^{1}H NMR ($CDCl_3$), δ 0.59 (t, J = 7.8 Hz, 6H), 1.01 (s, 9H), 2.00-2.28 (m, 4H), 2.17 (s, 3H), 2.41 (s, 3H), 3.00 (s, 3H), 3.35 (t, J = 5.6 Hz, 1H), 3.70 (bd, J = 8.6 Hz, 1H), 3.85 (t, J = 9.1 Hz, 1H), 3.97 (dd, J = 12.3, 5.6 Hz, 2H), 4.09 (dd, J = 9.1, 3.0 Hz, 1H), 6.53 (t, J = 5.9 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 6.85 (s, 1H), 6.91-7.01 (m, 2H), 7.25-7.29 (m, 2H). ES-MS (m/z): calcd for $C_{29}H_{44}NO_5S$ $(M + H)^+$: 518.7; found: 518.3.

Example 15A & 15B

Preparation of enantiomer 1 and 2 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]propyl}-N-(2-methanesulfonylethyl)-2-methylbenzamide.



(Enantiomer 1)

(Enantiomer 2)

A racemic mixture of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]propyl}-*N*-(2-methanesulfonylethyl)-2-methylbenzamide (0.34 g), Example 14, is chromatographed (HPLC: ChiralPak AD, 60% EtOH/Hept) to give enantiomer 1 (0.10 g, 29%, rt = 4.9 m) and enantiomer 2 (0.125 g, 37%, rt = 6.3 m).

Example 15A, 2071445 (enantiomer 1):

HPLC: ChiralPak AD (4.6 X 250 mm); 60% EtOH/Hept; 1.0 mL/m (flow rate); rt = 4.9 m; @ 240 nm.

NMR & LC/MS: equivalent to the racemate, Example 14.

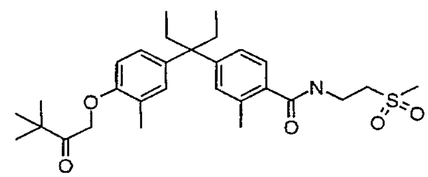
Example 15B, 2071447 (enantiomer 2):

HPLC: ChiralPak AD (4.6 X 250 mm); 60% EtOH/Hept; 1.0 mL/m (flow rate); rt = 6.3 m; @ 240 nm.

NMR & LC/MS: equivalent to the racemate, Example 14.

Example 16

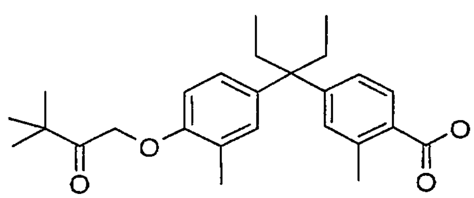
Preparation of 4-{1-[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]-1-ethylpropyl}-N-(2-methanesulfonylethyl)-2-methylbenzamide.



Using a procedure analogous to Example 13C, from 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]propyl}-*N*-(2-methanesulfonylethyl)-2-methylbenzamide, Example 14, (0.08 g, 0.16 mmol), NMO (27 mg, 0.24 mmol), and TPAP (2.8 mg, 0.08 mmol) are reacted for 1 h to give the title compound (0.06g, 76%). ^{1}H NMR ($CDCl_3$): δ 0.60 (t, J = 7.4 Hz, 6H), 1.27 (s, 9H), 2.05 (q, J = 7.4 Hz, 4H), 2.24 (s, 3H), 2.42 (s, 3H), 3.01 (s, 3H), 3.36 (t, J = 6.0 Hz, 2H), 3.94-4.02, (m, 2H), 4.82 (s, 2H), 6.46-6.57 (m, 2H), 6.82-7.23 (m, 5H). ES-MS (m/z): calcd for $C_{29}H_{42}NO_5S$ $(M + H)^+$: 516.7; found: 516.4.

Example 17

Preparation of 4-{1-[4-(3,3-dimethyl-2-oxobutoxy)-3-methylphenyl]-1-ethylpropyl}-2-methylbenzoic acid.

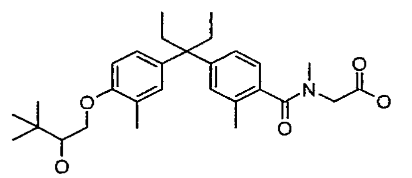


To a mixture of 4-{1-[4-(3,3-dimethyl-2-hydroxybutoxy)-3-methylphenyl]-1-ethylpropyl}-2-methylbenzoic acid, Example 1, (0.50 g, 1.22 mmol) in CH_2Cl_2 (10 mL) is added a solution of the Dess-Martin reagent (0.57 g, 1.34 mmol) in CH_2CL_2 (10 mL) dropwise and stirred for 2 h. The reaction is diluted with EtOAc (100 mL), washed with 10% Na_2SO_3 (2 x 20 ml), 0.1 M HCl (20 ml), and H_2O (20 ml). The organic layer is $MgSO_4$ dried, and concentrated to give the title compound (0.48 g, 1.17 mmol, 95%). ^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.2 Hz, 6H), 1.27 (s, 9H), 2.09 (q, J = 7.2 Hz, 4H), 2.25 (s, 3H), 2.61 (s, 3H), 4.85 (s, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.85-6.91 (m, 2H), 7.05-7.10

(m, 2H), 7.93 (d, $J = 9.0$ Hz, 1H). ES-MS (m/z): calcd for $C_{26}H_{38}NO_4$ $(M + NH_4)^+$: 428.6; found: 428.3.

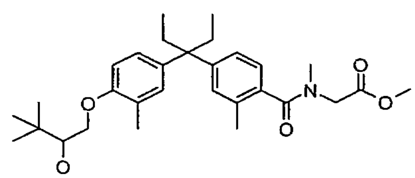
Example 18

Preparation of enantiomer 1 of [(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.



(Enantiomer 1)

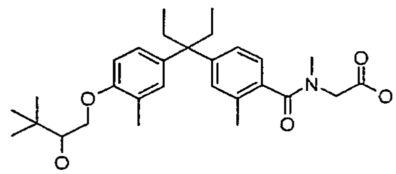
A. Enantiomer 1 of [(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester.



(Enantiomer-1)

Using a procedure analogous to Example 5, from enantiomer 1 of 4-(1-{4-[2-(hydroxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzoic acid, Example 3A, (1.28 g, 3.17 mmol) and *N*-methyl glycine methyl ester hydrochloride (0.48 g, 3.41 mmol) to give the title compound (1.43 g, 2.88 mmol, 93%). ^{1}H NMR ($CDCl_3$), δ 0.57-0.65 (m, 6H), 1.02 (s, 9H), 2.00-2.11 (m, 4H), 2.18 (s, 3H), 2.25 (s, 0.80H), 2.32 (s, 2.20H), 2.89 (s, 2.20H), 3.15 (s, 0.80H), 3.70 (s, 0.8H), 3.72 (d, $J = 2.6$ Hz, 1H), 3.79 (s, 2.2H), 3.86 (t, $J = 8.8$ Hz, 1H), 3.91 (s, 0.52H), 4.09 (dd, $J = 7.0, 2.6$ Hz, 1H), 4.32 (bs, 1.48H), 6.70 (d, $J = 8.3$ Hz, 1H), 6.85-7.11 (m, 5H). ES-MS (m/z): calcd for $C_{30}H_{44}NO_5$ $(M + H)^+$: 498.7; found: 498.3.

B. Enantiomer 1 of [(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid

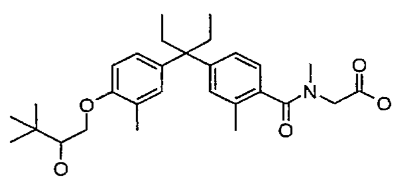


(Enantiomer 1)

Using a procedure analogous to Example 2, from enantiomer 1 of [(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester (1.43 g, 2.88 mmol) to give the title compound (1.24 g, 2.57 mmol, 90%). ^{1}H NMR ($CDCl_3$), δ 0.56-0.63 (m, 6H), 1.02 (s, 9H), 2.01-2.09 (m, 4H), 2.11 (s, 0.7H), 2.18 (s, 2.3H), 2.23 (s, 0.70H), 2.29 (s, 2.30H), 2.91 (s, 2.30H), 3.14 (s, 0.70H), 3.71 (dd, J = 8.8, 2.6 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 3.92(s, 0.47H), 4.09 (dd, J = 8.8, 2.6 Hz, 1H), 4.33 (bs, 1.53H), 6.69 (d, J = 8.8 Hz, 0.23H), 6.70 (d, J = 8.3 Hz, 0.77H), 6.85-7.11 (m, 5H). ES-MS (m/z): calcd for $C_{29}H_{40}NO_5$ (M - H)$^-$: 482.7; found: 482.3.

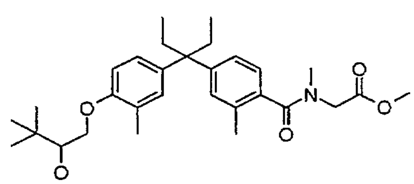
Example 19

Enantiomer 2 of [(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.



(Enantiomer 2)

A. Enantiomer 2 of [(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester.



(Enantiomer 2)

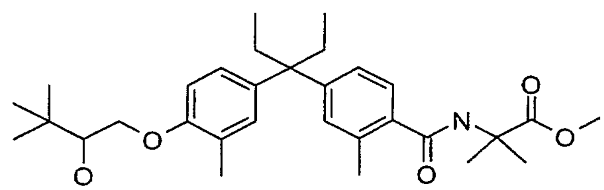
Using a procedure analogous to Example 5, from enantiomer 2 of 4-(1-{4-[2-(hydroxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzoic acid, Example 3B, (1.08 g, 2.62 mmol) to give the title compound (1.16 g, 2.33 mmol, 89%). ^{1}H NMR & LC/MS: equivalent to Example 18A.

B. Enantiomer 2 of [(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.

Using a procedure analogous to Example 2, from enantiomer 2 of [(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester (0.58 g, 1.16 mmol) givesthe title compound (0.53 g, 1.10 mmol, 95%). ^{1}H NMR & LC/MS: equivalent to Example 18B.

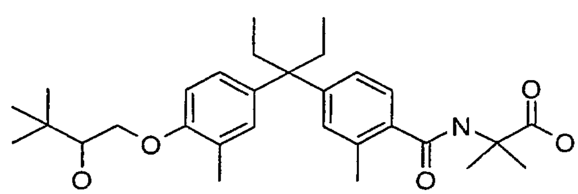
Example 20

A. 2-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-2-methyl-propionic acid methyl ester.



Using the procedure analogous to Example 5, from enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid, Example 3A, (0.40 g, 0.97 mmol) and 2-aminoisobutyric acid methyl ester hydrochloride (0.15 g, 1.07 mmol) to furnish the title compound (0.36 g, 0.70 mmol, 72 %). ^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.6 Hz, 6H), 1.01 (s, 9H), 1.64 (s, 6H), 2.01-2.09 (m, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 2.70 (d, J = 9.0 Hz, 1H), 3.77 (s, 3H), 3.85 (t, J = 9.1 Hz, 1H), 4.09 (d, J = 9.6 Hz, 1H), 6.28 (s, 1H), 6.70 (dd, J = 8.9, 2.6 Hz, 1H), 6.85 (s, 1H), 6.93 (d, J = 8.6 Hz, 1H), 6.95-7.02 (m, 2H), 7.27 (dd, J = 7.9, 2.6 Hz, 1H). ES-MS (m/z): calcd. for $C_{31}H_{46}NO_5$ $(M+H)^+$: 512.3; found: 512.3.

B. 2-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-2-methyl-propionic acid.

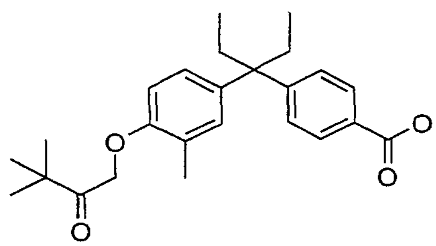


(Enantiomer 1)

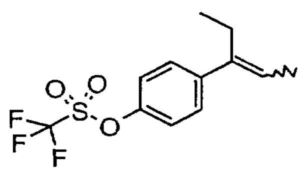
Using a procedure analogous to Example 2, from enantiomer 1 of 2-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-2-methyl-propionic acid methyl ester (0.36 g, 0.70 mmol) to furnish the titled compound (0.35 g, 0.70 mmol, 92%). ^{1}H NMR ($CDCl_3$), δ 0.59 (t, J = 7.3 Hz, 6H), 1.01 (s, 9H), 1.67 (s, 6H), 2.05 (q, J = 7.3 Hz, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 3.70 (dd, J = 8.7, 2.7 Hz, 1H), 3.86 (t, J = 8.9 Hz, 1H), 4.09 (dd, J = 9.1, 2.7 Hz, 1H), 6.28 (s, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 8.5, 2.3 Hz, 1H), 6.98-7.03 (m, 2H), 7.26 (d, J = 7.9 Hz, 1H). ES-MS (m/z): calcd. for $C_{30}H_{44}NO_5$ $(M+H)^+$: 498.3; found: 498.3.

Example 21

Preparation of 4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzoic acid.

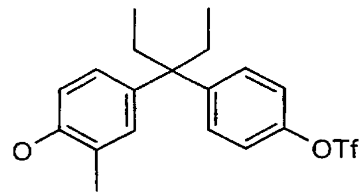


A. 4-(*Z/E*-2-Penten-3-yl)-*O*-trifluoromethylsulfonyl-phenol.



To a mixture of 4-(*Z/E*-2-penten-3-yl)phenol (7.45 g, 45.9 mmol), CH_2Cl_2 (150 mL), and Tf_2O (13.4 g, 47.5 mmol) is added DIPEA (6.13 g, 47.5 mol) drop wise. After stirring overnight, the reaction is poured into ice water (100 mL) and separated. The organic layer is washed with cold water (2 x 50 mL), Na_2SO_4 dried, filtered and concentrated to give the title compound as an oil (10.5 g, 78%) which is used as is.

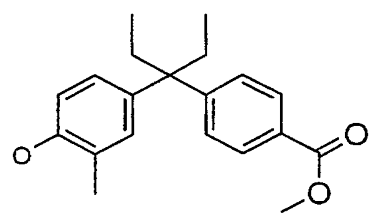
B. 4-[1-Ethyl-1-(3-methyl-4-hydroxyphenyl)propyl]-*O*-trifluoromethylsulfonylphenol.



To 4-(*Z/E*-2-penten-3-yl)-*O*-trifluoromethylsulfonyl-phenol (5.25 g, 17.8 mmol) and *O*-cresol (7.7 g, 71.4 mmol) in CH_2Cl_2 (20 mL) at –20 °C is added $BF_3 \cdot Et_2O$ (240 µL, 1.9 mmol), and the mixture is allowed to come to RT and stirred 16 h. To the reaction is added ethylene glycol (5 mL), and the CH_2Cl_2 is evaporated under vaccum. The residue is vacuum distilled up to 70 °C at 0.116 mm to remove the excess phenol and ethylene glycol. The residue is partitioned between Et_2O (50 mL) and water (50 mL). The organic layer is washed with water (3 x 50 mL), saturated brine, Na_2SO_4 dried, filtered and concentrated. The residue is chromatographed to give the title compound (3.9 g, 54%).

H-NMR ppm in $CDCl_3$: 7.24 (2H, d, J = 9.0 Hz); 7.14 (2H, d, J = 9.2 Hz); 6.84 (1H, s); 6.83 (1H, d, J = 8.0 Hz); 6.66 (1H, d, J = 8.0 Hz); 4.70 (1H, s); 2.20 (3H, s); 2.05 (4H, q, J = 7.2 Hz); 0.61 (6H, t, J = 7.2 Hz). LC-MS: 401.1 (M-1).

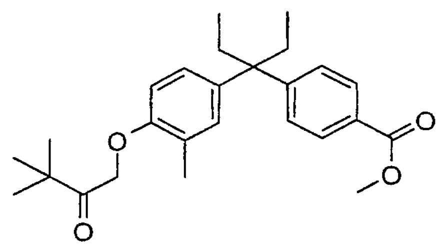
C. 4-[(1-Ethyl-1-(3-methyl-4-hydroxyphenyl)propyl]-benzoic acid, methyl ester.



Using a procedure analogous to Example 1E, from 4-[(1-ethyl-1-(3-methyl-4-hydroxyphenyl)propyl]-*O*-trifluoromethylsulfonylphenol (2.5 g, 6.2 mmol) gives the title compound (1.08 g, 56%).

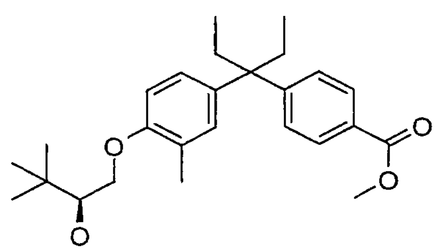
H-NMR ppm in $CDCl_3$: 7.89 (2H, d, J = 8.0 Hz); 7.23 (2H, d, J = 8.0 Hz); 6.84 (1H, s); 6.83 (1H, d, J = 8.2 Hz); 6.65 (1H, d, J = 8.2 Hz); 4.58 (1H, s); 3.89 (3H, s); 2.18 (3H, s); 2.08 (4H, q, J = 7.2 Hz); 0.61 (6H, t, J = 7.2 Hz). LC/MS: 313.1 (M+1), 311.1 (M-1).

D. 4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzoic acid methyl ester.



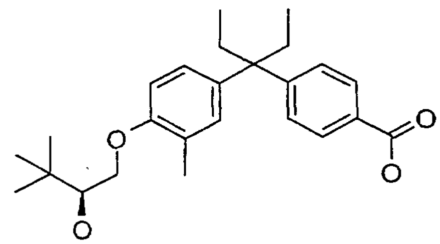
Using a procedure analogous to Example 1B, from 4-[(1-ethyl-1-(3-methyl-4-hydroxyphenyl)propyl]-benzoic acid, methyl ester (0.88 g, 2.81 mmol) gives the title compound (0.95 g, 2.32 mmol, 95%). ^{1}H NMR ($CDCL_3$), δ 0.61 (t, J = 7.4 Hz, 6H), 1.26 (s, 9H), 2.09 (q, J = 7.4 Hz, 4H), 2.24 (s, 3H), 3.89 (s, 3H), 4.84 (s, 2H), 6.49 (d, J = 8.8 Hz, 1H), 6.85-6.89 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 9.4 Hz, 2H). ES-MS (m/z): calcd for $C_{26}H_{38}NO_4$ $(M+NH_4)^+$: 428.6; found: 428.3.

E. 4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-benzoic acid methyl ester.



Using a procedure analogous to Example 1D, from 4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzoic acid methyl ester (0.94 g, 2.29 mmol) to give the title compound (0.93 g, 2.26 mmol, 99%). ^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.6 Hz, 6H), 1.02 (s, 9H), 2.10 (q, J = 7.6 Hz, 4H), 2.17 (s, 3H), 3.71 (dd, J = 8.8, 2.9 Hz, 1H), 3.86 (t, J = 8,6 Hz, 1H), 3.90 (s, 3H), 4.09 (dd, J = 9.3, 2.9 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.6 Hz, 2H). ES-MS (m/z): calcd for $C_{26}H_{37}O4$ $(M+H)^+$: 413.6; found: 413.3.

F. 4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}benzoic acid.



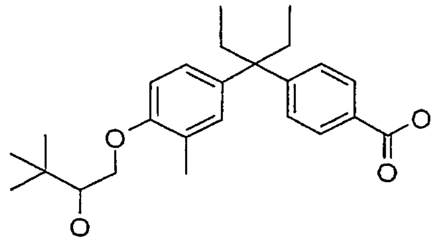
Using a procedure analogous to Example 2, from 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-benzoic acid methyl ester (0.93 g, 2.25 mmol) givesthe title compound (0.81 mmol, 2.02 mmol, 90%). ^{1}H NMR ($CDCl_3$), δ 0.63 (t, J = 7.2 Hz, 6H), 1.02 (s, 9H), 2.12 (q, J = 7.2 Hz, 4H), 2.18 (s, 3H), 3.71 (dd, J = 8.7, 2.4 Hz, 1H), 3.86 (t, J = 9.3 Hz, 1H), 4.09 (dd, J = 9.3, 2.4 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H). ES-MS (m/z): calcd for $C_{25}H_{33}O_4$ $(M-H)^-$: 397.6; found: 397.2.

G. 4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzoic acid.

Using a procedure analogous to Example 17, from 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}benzoic acid (0.31 g, 0.79 mmol) and Dess-Martin reagent (366 mg, 0.86 mmol) gives the title compound (0.27 g, 0.69 mmol, 88%). %). ^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.0 Hz, 6H), 1.27 (s, 9H), 2.10 (q, J = 7.0 Hz, 4H), 2.24 (s, 3H), 4.85 (s, 2H), 6.50 (d, J = 9.1 Hz, 1H), 6.85-6.90 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H). ES-MS (m/z): calcd for $C_{25}H_{31}O_4$ $(M-H)^-$: 395.6; found: 395.2.

Example 22 and 23

Preparation of enantiomer 1 and 2 of 4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}benzoic acid.



(Enantiomer-1)

(Enantiomer-2)

A racemic mixture of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}benzoic acid (500 mg) is chromatographed (CHIRALPAK AD column, Heptane, 90 %; EtOH, 9.5%, CH_3OH, 0.5%, TFA, 0.1%) to give enantiomer 1 (rt = 7.4 m), Example 22 (231 mg, 46%) and enantiomer 2 (rt = 9.4 m), Example 23 (230 mg, 46%).

Example 22, (Enantiomer 1):

rt = 7.4 m

NMR & LC/MS: Identical to the racemic material, Example 21F.

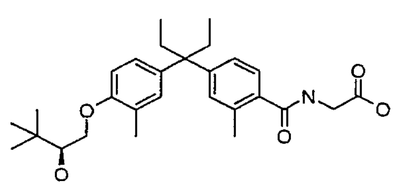
Example 23, (Enantiomer 2)

rt = 9.4 m

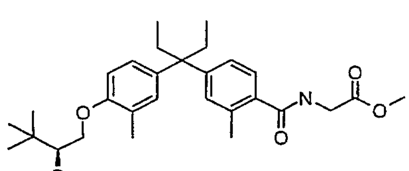
NMR & LC/MS: Identical to the racemic material, Example 21F.

Example 24

Preparation of (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzoylamino)acetic acid.



A. Methyl (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl] propyl}-2-methylbenzoylamino)acetate.



Using a procedure analogous to Example 5, from 4-(1-{4-[2-(hydroxy)-3,3-dimethyl-butoxy]-3-methylphenyl}-1-ethylpropyl)-2-methylbenzoic acid (0.50 g, 1.22 mmol) and glycine methyl ester hydrochloride (0.15 g, 1.22 mmol) give the title compound (0.587 g, 1.21 mmol, 99%).

^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.5 Hz, 6H), 1.03 (s, 9H), 2.07 (q, J = 7.5 Hz, 4H), 2.19 (s, 3H), 2.43 (s, 3H), 3.71 (dd, J = 8.8, 2.9 Hz, 1H), 3.80 (s, 3H), 3.87 (t, J = 8.8 Hz, 1H), 4.08-4.12 (m, 1H), 4.24 (d, J = 5.4 Hz, 1H), 6.26 (t, J = 5.4 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 8.5, 2.5 Hz, 1H), 6.99-7.04 (m, 2H), 7.32 (d, J = 7.8 Hz, 1H). ES-MS (m/z): calcd for $C_{29}H_{42}NO_5$ $(M + H)^+$: 484.7; found: 484.2.

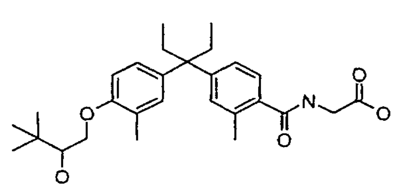
B. (4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzoylamino)acetic acid.

A mixture of methyl (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]propyl}-2-methylbenzoylamino)acetate (0.43 g, 0.89 mmol), CH_3OH (10 ml), NaOH (0.18 g, 4.46 mmol), and H_2O (1 mL) is refluxed for 2 h. The reaction is concentrated, diluted with H_2O (5 ml), acidified (pH 3-4) with 0.1 M HCl and extracted with EtOAc (3 x 15 mL). The combined organic layers are $MgSO_4$ dried, and concentrated to give the title compound (0.29 g, 71%).

^{1}H NMR (CD_3OD), δ 0.66 (t, J = 7.2 Hz, 6H), 1.05 (s, 9H), 2.15 (q, J = 7.2 Hz, 4H), 2.20 (s, 3H), 2.42 (s, 3H), 3.63-3.68 (m, 1H), 3.91 (dd, J = 10.0, 7.8 Hz, 1H), 4.09 (s, 2H), 4.16 (dd, J = 10.0, 2.9 Hz, 1H), 6.81 (d, J = 9.3 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 7.02 (dd, J = 8.4, 2.1 Hz, 1H), 7.09 (s, 1H), 7.11 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H). ES-MS (m/z): calcd for $C_{28}H_{40}NO_5$ $(M + H)^+$: 470.6; found: 470.2.

Example 25A and Example 25B

Preparation of enantiomer 1 and 2 of (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzoylamino)acetic acid.



(Enantiomer 1)

(Enantiomer 2)

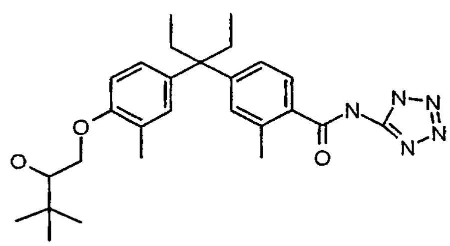
A racemic mixture of (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-propyl}-2-methylbenzoylamino)acetic acid (0.217 g), Example 24, is chromatographed (HPLC: ChiralPak AD, 0.1% TFA in 0.75:14.25:85 CH_3OH:EtOH:Hept) to give enantiomer 1 (80.6 mg, 37%, rt = 8.0 m) and enantiomer 2 (81.1 mg, 37%, rt = 10.1 m).

(Enantiomer 1), Example 25A:
HPLC: ChiralPak AD (4.6 X 250 mm); 0.1% TFA in 0.75:14.25:85 CH_3OH:EtOH:Hept; 1.0 mL/m (flow rate); rt = 8.0 m; @ 280 nm; 97.8% ee.
NMR & LC/MS: equivalent to the racemate, Example 24.

(Enantiomer 2), Example 25B:
HPLC: ChiralPac AD (4.6 X 250 mm); 0.1% TFA in 0.75:14.25:85 CH_3OH:EtOH:Hept; 1.0 mL/m (flow rate); rt = 10.1 m; @ 280 nm; 95.2% ee.
NMR & LC/MS: equivalent to the racemate, Example 24.

Example 26

Preparation enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 1)

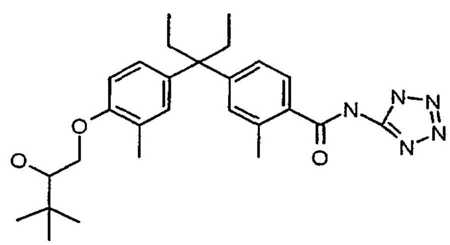
Using a procedure analogous to Example 5, enantiomer 1 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane and 5-aminotetrazole give the title compound (440 mg, 95%).
NMR 300 mHz (DMSO): 0.57 (t, J = 7.3 Hz, 6H), 0.92 (s, 9H), 2.09 (m, 7H), 2.40 (s, 3H), 3.46 (m, 1H), 3.76 (dd, J = 7.3, 10.2 Hz, 1H), 4.03 (dd, J = 3.3, 10.2 Hz, 1H),

4.79 (d, J = 5.5 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.89 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.12 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 12.23 (s, 1H), 16.00 (br s, 1H).

High Res. ES-MS: 480.2983; calc. for $C_{27}H_{37}N_5O_3$+H: 480.2975.

Example 27

Preparation enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



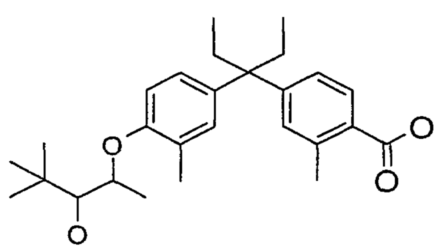
(enantiomer 2)

Using a procedure analogous to Example 5, enantiomer 2 of 3'-[4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane and 5-aminotetrazole gives the title compound (385 mg, 83%).

NMR 300 mHz (DMSO): eq. to enantiomer of 1.

High Res. ES-MS: 480.2968; calc. for $C_{27}H_{37}N_5O_3$+H: 480.2975.

Preparation of 4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid.



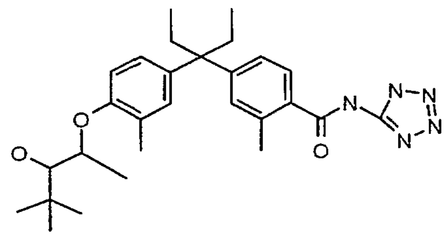
(Racemic)

Using a procedure analogous to Example 2, from racemic 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid methyl ester, Example 10C, (4.70 g, 10.68 mmol) gives the title compound (2.93 g, 6.87 mmol, 64%).

^{1}H NMR and ES-MS: equivalent to the pure enantiomer 1, Example 11.

Example 29

Preparation enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 1)

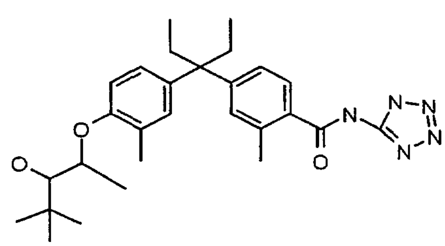
Using a procedure analogous to Example 5, enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, Example 11, and 5-aminotetrazole give the title compound (125 mg, 72%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.57 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), 1.20 (d, J = 6.3 Hz, 3H), 2.07 (m, 7H), 2.41 (s, 3H), 3.07 (br s, 1H), 4.37 (br s, 1H), 4.57 (q, J = 5.8, 1H), 6.87 (m, 3H), 7.06 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 12.24 (s, 1H), 16.0 (s, 1H).

High Res ES(+)MS m/z: 494.3127; calc. for $C_{28}H_{39}N_5O_3$ + H: 494.3131

Example 30

Preparation enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(tetrazol-5-ylaminocarbonyl)-3-methylphenyl]pentane.



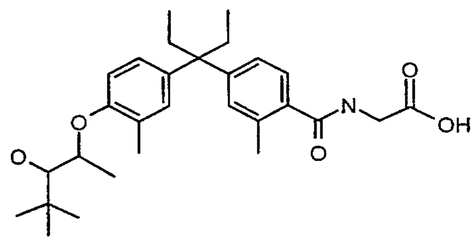
(enantiomer 2)

Using a procedure analogous to Example 5, enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, Example 12, and 5-aminotetrazole give the title compound (150 mg, 74%).

High Res ES(+)MS *m/z*: 494.3144; calc. for $C_{28}H_{39}N_5O_3$ + H: 494.3131

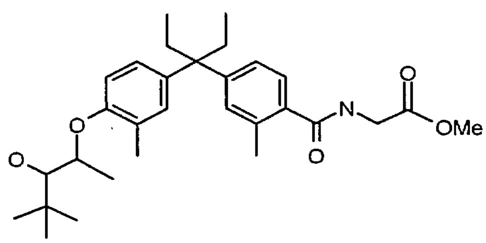
Example 31

Preparation enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 1)

A. Enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 1)

Using a procedure analogous to Example 5, enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, methyl glycinate hydrochloride, and DMAP (2.5 eq) give the title compound (150 mg, 86%). ^{1}H NMR 400 MHz (DMSO-d_6): δ 0.55 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), 1.20 (d, J = 5.9 Hz, 3H), 1.98-2.07 (m, 7H), 2.32 (s, 3H), 3.07 (s, 1H), 3.65 (s, 3H), 3.93(d, J = 6.3 Hz, 2H), 4.36 (br s, 1H), 4.55 (q, J = 7.2 Hz, 1H), 6.80-6.84 (m, 2H), 6.89 (d, J = 8.3 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.05 (s, 1H), 7.24 (d, J = 8.3 Hz, 1H), 8.61 (t, J = 5.9 Hz, 1H). High Res ES(+)MS *m/z*: 498.3224; calc. for $C_{30}H_{43}NO_5$ + H: 498.3219.

B. Enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.

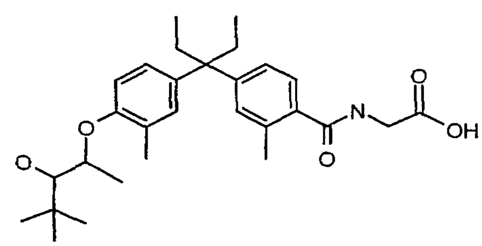
Using a procedure analogous to Example 2 but reacted at RT, enantiomer 1 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane gives the title compound (130 mg, 99%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.55 (t, J = 7.3 Hz, 6H), 0.91 (s, 9H), 1.20 (d, J = 5.9 Hz, 3H), 1.98-2.07 (m, 7H), 2.32 (s, 3H), 3.07 (s, 1H), 3.84 (d, J = 5.8 Hz, 2H), 4.37 (br s, 1H), 4.56(q, J = 6.3 Hz, 1H), 6.80-6.84 (m, 2H), 6.89 (dd, J = 2.4, J = 8.3 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 7.04 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H)

High Res ES(+)MS *m/z*: 484.3041; calc. for $C_{29}H_{41}NO_5$ + H: 484.3063

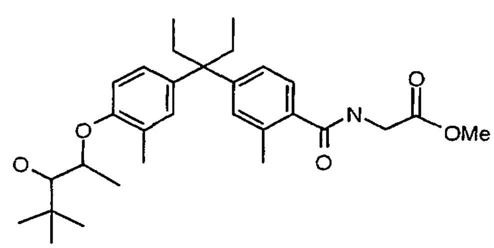
Example 32

Preparation enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 2)

A. Enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane.



(enantiomer 2)

Using a procedure analogous to Example 5, enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane, methyl glycinate hydrochloride, and DMAP (2.5 eq) give the title compound (160 mg, 78%). NMR equivalent to Example 31A.

High Res ES(+)MS m/z: 498.3200; calc. for $C_{30}H_{43}NO_5$ + H: 498.3219

B. Enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(carboxymethylaminocarbonyl)-3-methylphenyl]pentane.

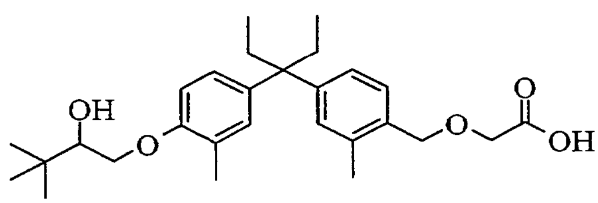
Using a procedure analogous to Example 2 but reacted at RT, enantiomer 2 of 3'-[4-(2-hydroxy-1,3,3-trimethylbutoxy)-3-methylphenyl]-3'-[4-(methoxycarbonylmethylaminocarbonyl)-3-methylphenyl]pentane gives the title compound (145 mg, quant).

NMR equivalent to Example 31B.

High Res ES(+)MS m/z: 484.3080; calc. for $C_{29}H_{41}NO_5$ + H: 484.3063

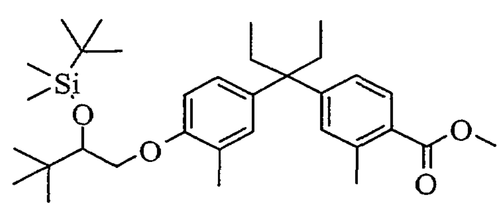
Example 33

Preparation of enantiomer 1 of (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyloxy)-acetic acid.



(enantiomer 1)

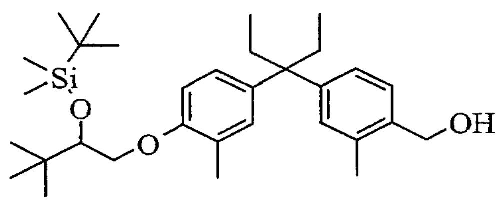
A. Enantiomer 1 of 4-(1-{4-[2-(tert-butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-benzoic acid methyl ester.



(enantiomer 1)

Using a procedure analogous to Example 13A, from enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid methyl ester (1.90 g, 4.45 mmol to furnish the title compound (2.40 g, 4.45 mmol, >99%). ^{1}H NMR & ES-MS: equivalent to (Example 13A).

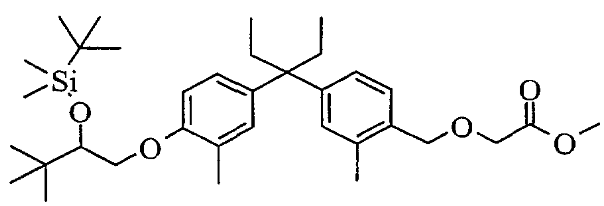
B. Enantiomer 1 of [4-(1-{4-[2-(tert-butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-phenyl]-methanol.



(enantiomer 1)

Using a procedure analogous to 13B, from enantiomer 1 of 4-(1-{4-[2-(tert-butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-benzoic acid methyl ester (2.40 g, 4.45 mmol) to furnish the title compound (2.10 g, 4.09 mmol, 91%).
^{1}H NMR & ES-MS: equivalent to (Example 13B).

C. [4-(1-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-benzyloxy]-acetic acid methyl ester.



(enantiomer 1)

To a solution of enantiomer 1 of [4-(1-{4-[2-(tert-butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-phenyl]-methanol, (2.10 g, 4.10 mmol) and $PhCH_3$ (10 mL) is added methyl glycolate (6.5 mL, 81.89 mmol) and $MeReO_3$ (0.02 g, 0.082 mmol). The solution is heated at a reflux for 2 hours with the use

of a Dean-Stark trap. The solution is concentrated and chromatographed to give the title compound (0.96 g, 1.64 mmol, 40%).

^{1}H NMR ($CDCl_3$), δ 0.06 (s, 3H), 0.11 (s, 3H), 0.61 (t, J = 7.3 Hz, 6H), 0.90 (s, 9H), 0.97 (s, 9H), 2.05 (q, J = 7.3 Hz, 4H), 2.18 (s, 3H), 2.33 (s, 3H), 3.67 (dd, J = 5.7, 3.2 Hz, 1H), 3.77 (s, 3H), 3.85 (dd, J = 9.7, 5.7 Hz, 1H), 3.98 (dd, J = 9.7, 3.5 Hz, 1H), 4.12 (s, 2H), 4.60 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.92 (dd, J = 8.4, 2.6 Hz, 1H), 6.97-7.01 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H).).

D. Enantiomer 1 of (4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyloxy)-acetic acid.

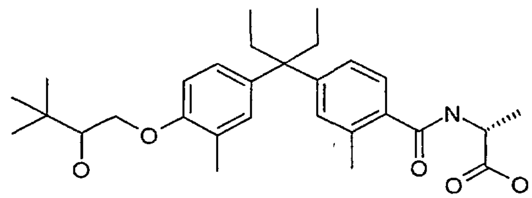
To a solution of enantiomer 1 of [4-(1-{4-[2-(tert-butyl-dimethyl-silanyloxy)-3,3-dimethyl-butoxy]-3-methyl-phenyl}-1-ethyl-propyl)-2-methyl-benzyloxy]-acetic acid methyl ester (0.96 g, 1.64 mmol) and THF (10 mL) is added 1M TBAF (3.3 mL, 3.28 mmol). The solution is heated at a reflux overnight and concentrated. The residue is dissolved in MeOH (5 mL) and water (1 mL), NaOH (0.33 g, 8.21 mmol) is added and the solution is heated at reflux for 3 hours. The solution is concentration, dissolved in EtOAc (20 mL), washed with 1M HCl (15 mL), water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. The residue is chromatographed to furnish the title compound (0.45 g, 0.99 mmol, 60%).

^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.3 Hz, 6H), 1.02 (s, 9H), 2.05 (q, J = 7.3 Hz, 4H), 2.17 (s, 3H), 2.31 (s, 3H), 3.71 (dd, J = 8.8, 2.6 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 4.09 (dd, J = 8.8, 2.6 Hz, 1H), 4.13 (s, 2H), 4.62 (s, 2H), 6.70 (d, J = 8.3 Hz, 1H), 6.90-7.02 (m, 4H), 7.16 (d, J = 7.5 Hz, 1H).

ES-MS (m/z): calcd. for $C_{28}H_{41}O_6$ $(M-H)^-$: 455.6; found: 455.2.

Example 34

Preparation of epimer 1 of *D*-2-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.



(D-Epimer 1)

A. Epimer 1 of *D*-2-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester.

(D-Epimer 1)

Using a procedure analogous to Example 5, from enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.40 g, 0.97 mmol) and *D*-alanine methyl ester hydrochloride (0.15 g, 1.07 mmol) to furnish the title compound (0.36 g, 0.72 mmol, 75%).

^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.2 Hz, 6H), 1.00 (s, 9H), 1.49 (d, J = 7.1 Hz, 3H), 2.05 (q, J = 7.2 Hz, 4H), 2.17 (s, 3H), 2.40 (s, 3H), 3.69 (dd, J = 8.5, 2.7 Hz, 1H), 3.76 (s, 3H), 3.84 (t, J = 9.1 Hz, 1H), 4.07 (dd, J = 9.1, 2.5 Hz, 1H), 4.72-4.81 (m, 1H), 6.42 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.4, 2.4 Hz, 1H), 6.96-7.01 (m, 2H), 7.28 (d, J = 8.1 Hz, 1H).

ES-MS (m/z): calcd. for $C_{30}H_{44}NO_5$ $(M+H)^+$: 498.3; found: 498.3.

B. Epimer 1 of *D*-2-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.

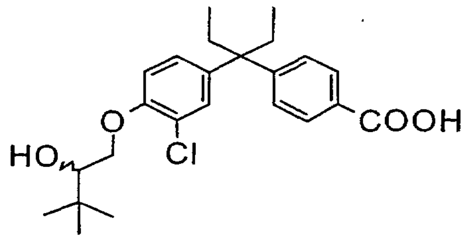
Using a procedure analogous to Example 2, from epimer 1 of *D*-2-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester (0.36 g, 0.72 mmol) to furnish the titled compound (0.31 g, 0.64 mmol, 89 %).

^{1}H NMR ($CDCl_3$), δ 0.60 (t, J = 7.5 Hz, 6H), 1.01 (s, 9H), 1.50 (d, J = 7.3 Hz, 3H), 2.05 (q, J = 7.5 Hz, 4H), 2.17 (s, 3H), 2.41 (s, 3H), 3.71 (dd, J = 8.4, 2.5 Hz, 1H), 3.85 (t, J = 8.9 Hz, 1H), 4.09 (dd, J = 9.3, 2.7 Hz, 1H), 4.74-4.83 (m, 1H), 6.33 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.93 (dd, J = 8.2, 2.2 Hz), 6.98-7.03 (m, 1H), 7.01 (s, 1H), 7.30 (d, J = 8.0 Hz, 1H).

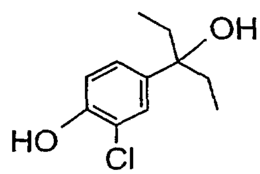
ES-MS (m/z): calcd. for $C_{29}H_{42}NO_5$ $(M+H)^+$: 484.3; found: 484.3.

Example 35.

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[4-carboxyphenyl]pentane.



A. 3-(3-Chloro-4-hydroxyphenyl)-3-pentanol.



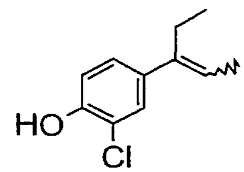
To a solution of methyl 3-chloro-4-hydroxybenzoate (25.0 g, 133 mmol) in THF (250 mL) is added dropwise 1.0 M ethylmagnesium bromide/THF (442 mL, 442 mmol) at a rate maintaining the temperature below 27 °C. The brownish grey reaction is stirred for 72 h. The reaction mixture is cooled in an ice bath and quenched with satd ammonium chloride (1 ml portions) until evolution of ethane subsides. Additional satd NH4Cl solution is added (total of 50mL) and the mixture is concentrated to remove most of the THF. The residue is added to water and ether, filtered through diatomaceous earth, and partitioned. The organic layer is washed with brine (3 X), MgSO4 dried, and concentrated to give the title compound (28.6 g, 99%).

H-NMR (300 mHz, CDCl3): δ 7.38 (1H, d, J = 1.6 Hz), 7.07 (1H, dd, J = 8.4 Hz, J = 1.6 Hz), 6.95 (1H, d, J = 8.4 Hz), 5.53 (1H, br s), 1.80 (4H, m), 0.76 (6H, t, J = 7.6 Hz).

IR (CHCl3): 3600 cm^{-1}, 3540 cm^{-1}.

EI (+) TOF MS: Observed m/z 214.076; Calc. m/z. 214.0761

B. [E, Z]-3-(3-Chloro-4-hydroxyphenyl)-3-pentene

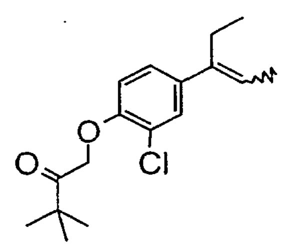


A mixture of 3-(3-chloro-4-hydroxyphenyl)-3-pentanol (10.0 g, 46.5 mmol), pTSA monohydrate (20 mg, catalytic amount), and toluene (300 mL) is heated on a steam bath for 3 h. Analysis by TLC indicates the loss of starting material and formation of a much less polar compound. The toluene solution is cooled to RT, washed with satd sodium carbonate solution (25 mL), MgSO4 dried, and concentrated to give the title compounds as a [E:Z] isomeric mixture of [85:15] (9.2 g, quant).

TLC (CHCl3): Rf ~0.7

H-NMR (300 mHz, DMSO-d6): δ 6.85-7.30 (3H, m), 5.65 (0.85H, q, J = 6.8 Hz), 5.43 (0.15H, q, J = 6.8 Hz), 2.43((1.7H, q, J = 7.6 Hz), 2.28 (0.3H, q, J = 7.6 Hz), 1.72 (2.55H, d, J = 7.6 Hz), 1.52 (0.45H, d, J = 7.6 Hz), 0.90 (2.55H, t, J = 7.6 Hz) 0.85 (0.45H, t, J = 7.6 Hz)

C. [E,Z]-3-[3-Chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene



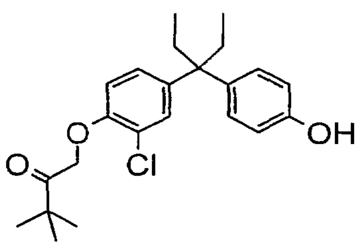
A mixture of [E,Z]-3-(3-chloro-4-hydroxyphenyl)-3-pentene (4.00 g, 20.3 mmol) and 1-chloropinacolone (2.73 g, 20.3 mmol), anhydrous KI (0.17 g, 1.0 mmol), K2CO3 (14.0 g, 102 mmol) and acetonitrile (80 mL) is refluxed for 3 h. The reaction is cooled to RT and concentrated. The residue is partitioned between methylene chloride (50 mL) and ice water (50 mL). The organic layer is MgSO4 dried, concentrated, and chromatographed (40% to 70% chloroform in hexane) to give the title compounds as an 85 : 15 [E. Z] mixture (5.07 g, 85%).

H-NMR (300 mHz, DMSO-d6): δ 7.37 (0.85H, d, J = 2.1 Hz), 7.22 (0.85H, dd, J=2.1, J = 8.6 Hz), 7.18 (0.15H, d, J = 2.1 Hz), 7.03 (0.15H, dd, J = 2.0 Hz, J = 8.4 Hz), 6.88

(0.15H, d, J = 8.4 Hz), 6.85 (0.85H, d, J = 8.6 Hz), 5.71 (0.85H, m), 5.52 (0.15H, m), 5.25 (2H, s), 2.45 (1.70H, q, J = 7.6 Hz), 2.30 (0.30H, q, J = 7.6 Hz), 1.75 (2.55H, d, J = 7.6 Hz), 1.53 (0.45H, d, J = 7.6 Hz), 1.17 (9H, s), 0.91 (2.55H, t, J = 7.6 Hz), 0.88 (0.45H, t, J = 7.6 Hz).

EI (+) TOF MS: Observed m/z 294.139; Calc. m/z 294.1387.

D. 3'-[3-Chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane.

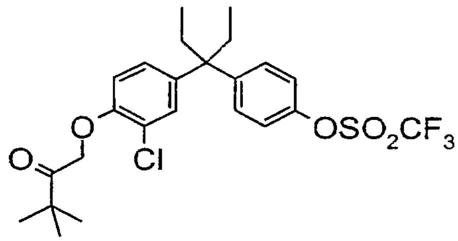


A -20 °C solution of [E,Z]-3-[3-chloro-4-(2-oxo-3,3-dimethylbutoxy)phenyl]-3-pentene (4.5 g, 15.2 mmol), phenol (17.2 g, 183 mmol) and methylene chloride (30 mL) is treated with BF3-etherate (0.863 g, 6.1 mmol) and stirred for 30 m while maintaining the temperature near –20 °C. The resulting light reddish brown solution is allowed to warm to 0 °C and kept at that temperature for 16 h. The reaction is distilled at 45 °C/0.04 mm to remove most of the excess phenol. The residue is treated with powderized NaHCO3 (600 mg), ethylene glycol (15 ml), and distilled to remove the last of the phenol and almost all of the glycol. The resulting viscous tan oily residue is cooled to RT and distributed between sat NaHCO3 (25 mL) and ethyl acetate (200 mL). The organic layer is separated, washed with water (5 x 50 mL), Na2SO4 dried, and concentrated to give the title compound as an oil (5.8 g, 98%).

H-NMR (300 mHz, CDCl3): 7.21 (1H, d, J = 2.3 Hz), 6.99 (2H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.75 (2H, d, J = 8.7 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 4.86 (1H, s), 2.02 (4H, q, J = 7.3 Hz), 1.28 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

ES(+) MS m/z: 389.3 [M+H]; calc. m/z 389.1883 [M+H].

E. 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)]-3'-(4-trifluoromethylsulfonyloxyphenyl)pentane.



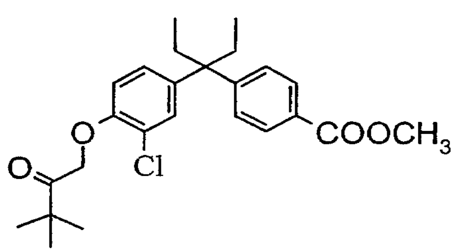
Using a procedure analogous to Example 1C with isopropyldiethylamine as the base, allowing the reaction to warm from 0 to RT overnight, and with potassium phosphate monobasic/sodium hydroxide buffer quench, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-(4-hydroxyphenyl)pentane and triflic anhydride give the title compound as a colorless oil (3.7g, 69%).

H-NMR (300 mHz, DMSO-D6): δ 7.40 (2H, d, J = 8.7 Hz), 7.33 (2H, d, J = 8.7 Hz), 7.15 (1H, d, J = 2.1 Hz), 6.98 (1H, dd, J = 2.1 Hz, J = 8.6 Hz), 6.78 (2H, d, J = 8.6 Hz), 5.22 (2H, s), 2.07 (4H, q, J = 7.3 Hz), 1.17 (9H, s), 0.55 (6H, t, J = 7.3 Hz).

FAB+ MS m/z: 521.0 [M+H]; calc. 521.1376 [M+H].

ES MS: 521.3 [M+1], 538.3 [M+NH4], 543.2 [M+Na].

F. 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-chloro-phenyl]-3'-4-carbomethoxyphenyl)-pentane.



To 3'-[4-(2-oxo-3,3-dimethylbutoxy)-3-chlorophenyl]-3'-(4-trifluoromethyl-sulfonyloxy-phenyl)-pentane (3.7 g 7.1 mmol), palladium acetate (64 mg, 0.28 mmol), dppf (315 mg, 0.28 mmol), and triethylamine (4 mL) are heated in the absence of air under an atmosphere of carbon monoxide (initial 100 psig) in DMF (20 mL) and methanol (2 mL) at 110 °C for 48 h. The reaction mixture is cooled to room temperature,

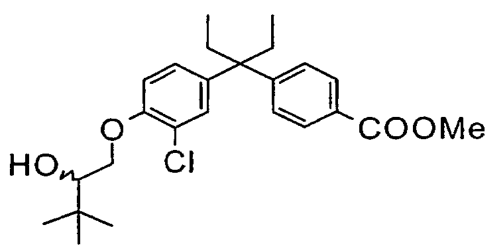
vented, and filtered. The filtrate is partitioned between EtOAc and water. The organic phase is washed 3 times with water, once with sat brine, dried over anhydrous Na2SO4, and concentrated under vacuum. The residue is chromatographed on 10 g silica gel with 8% EtOAc in hexanes to give the title compound (1.12 g, 37%).

H-NMR (400 mHz, CDCl3): δ 7.91 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz), 7.16 (1H, s), 6.88 (1H, d, J = 8.8 Hz), 6.59 (1H, d, J = 8.8 Hz), 4.90 (2H, s), 3.89 (3H, s), 2.07 (4H, q, J = 7.2 Hz), 1.25 (9H, s), 0.61 (6H, t, J = 7.2 Hz).

FAB(+) MS m/z [M]: 431.1; calc. m/z 431.3.

ES (+) MS: m/z 431.3 [M+H], 448.3 [M+NH4].

G. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[4-carbomethoxyphenyl]pentane.



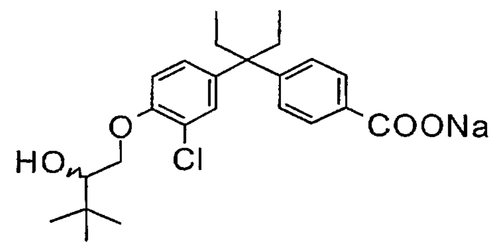
A solution of 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-chloro-phenyl]-3'-(4-methoxycarbonyl-phenyl)-pentane (0.825 g, 1.91 mmol) in MeOH (10 mL) under a N2 atmosphere is cooled to 0 °C. Sodium borohydride (0.076g, 2.01 mmol) is added in one portion and the reaction mixture is stirred for 15 minutes. Acetone (1 mL) followed by potassium phosphate monobasic/sodium hydroxide buffer (3 mL) are added and the resulting mixture is concentrated to remove most of the MeOH. The residue is distributed into water and CH2Cl2 and the organic layer is separated and dried over anhydrous MgSO4. The desired product is obtained as a colorless oil, (0.816 g, 98.5%).

H-NMR (300 mHz, CDCl3): δ 7.92 (2H, d, J = 8.8 Hz), 7.22 (2H, m), 7.15 (1H, d, J = 2.3), 6.93 (1H, dd, J = 2.3 Hz, J = 8.8 Hz), 6.84 (1H, d, J = 8.8 Hz), 4.17 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.89 (s, 3H), 3.87 (t, J = 8.9 Hz,), 3.62 (1H, dt, J = 2.6, J = 8.9, J = 3.0), 2.60, (1H, d, J = 3.0 Hz), 2.09 (4H, q, J = 7.3 Hz), 1.01 (9H, s), 0.61 (6H, t, J = 7.3 Hz).

FAB(+) MS m/z [M]: 432.2; calc. for C25H33ClO4: m/z 432.2.

IR (CHCl3): 1718 cm^{-1}

H. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[4-carboxyphenyl]pentane, sodium salt.



The methyl ester of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethyl-butoxy)phenyl]-3'-[4-(carboxy)phenyl]pentane (0.600 g, 1.38 mmol) and 2N NaOH (3.46 mL, 6.93 mmol) are refluxed in EtOH (15mL) under a N2 atmosphere for 1 h. TLC (SiO2; CHCl3) shows the loss of the starting material and appearance of a more polar compound spot near the origin. The reaction is allowed to cool to near RT and subsequently it is concentrated under reduced pressure to remove EtOH and provide a white residue. The residue is dissolved in a minimum amount of hot water (approx. 20 mL) and cooled and scratched to provide the desired sodium salt as white crystals (0.582 g, 96%).

H-NMR (300 mHz, DMSO): δ 7.73 (2H, d, J = 8.7 Hz), 7.00 to 7.06 (5H, m), 4.88 (1H, d, J = 5.1 Hz), 4.10 (1H, dd, J = 3.0 Hz, J = 10.2 Hz), 3.86 (1H, dd, J = 3.1 Hz, J = 10.2 Hz), 3.47 (1H, m), 2.04 (4H, q, J = 7.3 Hz), 0.92 (9H, s), 0.55 (6H, t, J = 7.3 Hz).

ES (+) MS m/z 436.2 [M+NH4], 441.1 [M+Na]

ES (-) MS m/z 417.2 [M-H].

IR (CHCl3): 1601 cm^{-1}.

I. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[4-carboxyphenyl]pentane.

A portion of the above 3'-[3-chloro-4-(2-hydroxy-3,3-dimethyl-butoxy)phenyl]-3'-[4-(carboxy)phenyl]pentane, sodium salt (0.182 g, 0.413 mmol) is dissolved in 50 ml of hot water. After the solution is allowed to cool to near to RT it is acidified with dropwise addition of 5N HCl. The resulting white precipitate is

collected and washed with ice water and subsequently vacuum dried to provide the desired free acid (0.169 g, 98%).

H-NMR (300 mHz, DMSO): δ 7.85 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.3) 7.00 to 7.12 (3H, m), 4.85 (1H, d, J = 5.1 Hz), 4.11 (1H, dd, J = 3.0 Hz, J = 10.2 Hz), 3.87 (1H, dd, J = 3.1 Hz, J = 10.2 Hz), 3.47 (1H, m), 2.08 (4H, q, J = 7.3 Hz), 0.94 (9H, s), 0.56 (6H, t, J = 7.3 Hz).

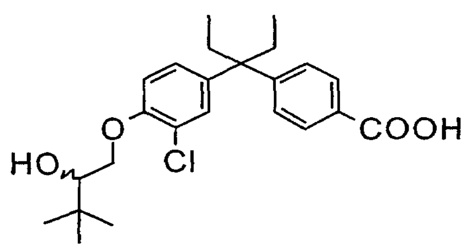
ES (+) MS: 436.2 [M+NH4], 441.1 [M+Na]

ES (-) MS: 417.2 [M-1].

IR (CHCl3): 1691 cm^{-1}.

Example 36 and 37

Separation of optical isomers of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[4-carboxyphenyl]pentane.



(isomer 1)

(isomer 2)

A racemic mixture of the Na salt of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-4-carboxyphenyl)pentane (350 mg) is chromatographed with a Chiralpak AD column to give enantiomer 1, Example 36 (120 mg, 36%) and enantiomer 2, Example 37 (117 mg, 35%).

Example 36, Enantiomer 1

HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 7.3 m; 240 nm; ee 99.7% by HPLC.

H-NMR (300 mHz, DMSO): δ 7.85 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.3) 7.00 to 7.12 (3H, m), 4.85 (1H, d, J = 5.1 Hz), 4.11 (1H, dd, J = 3.0 Hz, J = 10.2 Hz), 3.87 (1H, dd, J = 3.1 Hz, J = 10.2 Hz), 3.47 (1H, m), 2.08 (4H, q, J = 7.3 Hz), 0.94 (9H, s), 0.56 (6H, t, J = 7.3 Hz).

ES (+) MS: 436.2 [M+NH4], 441.1 [M+Na]
ES (-) MS: 417.2 [M-1].

Example 37, Enantiomer 2

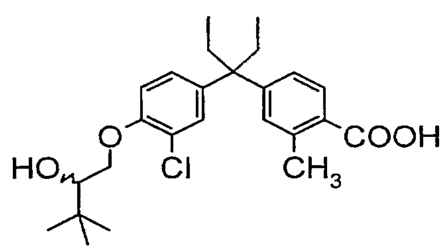
HPLC: Chiralpak AD (4.6 X 150 mm); 100% 3A Alcohol; 0.6 mL/m (flow rate); rt = 10.5 m; 240 nm; ee 99.0% by HPLC.

H-NMR (300 mHz, DMSO): δ 7.85 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.3) 7.00 to 7.12 (3H, m), 4.85 (1H, d, J = 5.1 Hz), 4.11 (1H, dd, J = 3.0 Hz, J = 10.2 Hz), 3.87 (1H, dd, J = 3.1 Hz, J = 10.2 Hz), 3.47 (1H, m), 2.08 (4H, q, J = 7.3 Hz), 0.94 (9H, s), 0.56 (6H, t, J = 7.3 Hz).

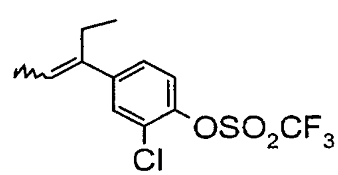
ES (+) MS: 436.2 [M+NH4], 441.1 [M+Na]
ES (-) MS: 417.2 [M-1].

Example 38

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carboxy)phenyl]pentane.



A. [E,Z]-3-[3-Chloro-4-(trifluoromethylsulfonyloxy)phenyl)-3-pentene.

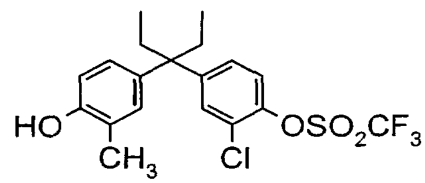


Using a procedure analogous to Example 1C, [E, Z]-3-(3-chloro-4-hydroxyphenyl)-3-pentene, triflic anhydride, and diisopropylethylamine are reacted at RT for 3 h to give the title compound as a yellow oil in a [E:Z] ratio of 9:1 (16.7 g, 98%). Chromatography over silica gel using 10% chloroform in hexane as the eluent provided 11.72 g (71.%) of purified material.

H-NMR (300 mHz, CDCl3): δ 7.01-7.39 (3H, m), 5.70 (0.9H, q, J = 6.9 Hz), 5.53 (0.1H, q, J = 6.9 Hz), 2.41((1.8H, q, J = 7.6 Hz), 2.24 (0.2H, q, J = 7.6 Hz), 1.74 (2.7H, d, J = 7.6 Hz), 1.48 (0.3H, d, J = 7.6 Hz), 0.91 (2.7H, t, J = 7.6 Hz)), 0.89 (0.3H, t, J = 7.6 Hz).

ES GC MS m/z 328.0 ; Calc. for C12H12ClF3O3S m/z 328.0148.

B. 3'-(4-hydroxy-3-methylphenyl)-3'-[3-chloro-4-(trifluoromethylsulfonyloxy)-phenyl]pentane.



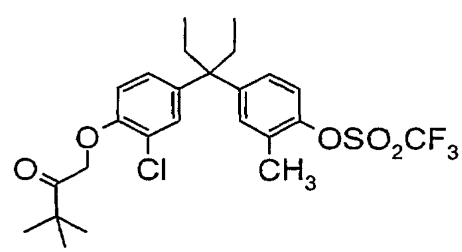
Using a procedure analogous to Example 35D, [E,Z]-3-[3-chloro-4-(trifluoromethylsulfonyloxy)phenyl]-3-pentene and o-cresol are reacted at RT overnight to give the title compound as a pale tan oil (4.29g, 38%).

H-NMR (300 mHz, CDCl3): 6.5 to 7.3 (6H, m) 4.57 (1H,s), 2.21 (3H, s), 2.05 (4H, q, J = 7.3 Hz), 0.62 (6H, t, J =7.3 Hz).

ES (-) MS m/z 435.1 [M-H].

C. 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)-phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane.

Triflate Rearrangement Procedure.



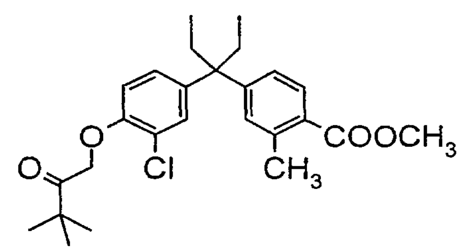
Using a procedure analogous to Example 35C, 3'-(3-chloro-4-hydroxyphenyl)-3'-[3-methyl-4-(trifluoromethylsulfonyloxy)phenyl]pentane, 1-chloropinacolone, anhydrous KI, and K2CO3 are reacted in acetonitrile to give the title compound (2.61 g, 53%) following chromatographies (30% to 50% chloroform/Hex; Hex to 10% EtOAc/Hex).

H-NMR (300 mHz, CDCl3): δ 7.15 (1H, d, J = 2.3 Hz), 7.11 (1H, d, J= 8.4 Hz), 7.04 (1H, d, J = 2.3 Hz), 7.02 (1H, dd, J = 2.3 Hz, J = 8.4 Hz), 6.89 (1H, dd, J = 8.6 Hz, J = 2.3 Hz), 6.62 (1H, d, J = 8.6 Hz), 4.91 (2H, s), 2.32 (3H, s), 2.03 (4H, q, J = 7.2 Hz), 1.26 (9H, s), 0.60 (6H, t, J = 7.2 Hz).

ES (+) MS m/z, [M+NH4]: 552.2.

Further NMR data: COSY data allowed the spin systems of the two aromatic rings to be grouped together. When the OCH2 was selectively excited, a NOE is observed with a resonance at 6.62 δ which is ortho only coupled. When the aromatic methyl (at 2.32 δ) was excited, a NOE is observed to a meta coupled proton at 7.04 δ. These resonances are not part of the same spin system, requiring the OCH2 and aromatic methyl to be on different rings. Therefore the triflate has migrated during the reaction and the isolated product has the structure shown above. (HMBC data also supports this conclusion.)

D. 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carbomethoxy)phenyl]pentane.



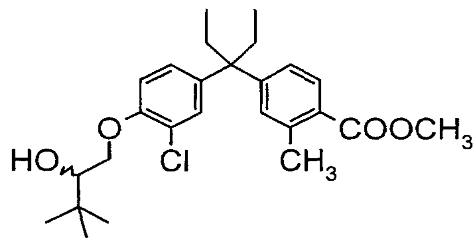
Using a procedure analogous to Example 35F, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)-phenyl]-3'-[3-methyl-4-(trifluoromethylsulfonyl-oxy)phenyl]pentane, MeOH, dppb, DMSO, Et3N, and Pd(OAc)2 under an atmosphere of CO are reacted to provide the title compound as a colorless oil (938 mg, 73%).

H-NMR (300 mHz, CDCl3): δ 7.82 (1H, d, J = 8.8 Hz), 7.20 (1H, d, J= 2.3 Hz), 7.03 – 7.05 (2H, m), 6.92 (1H, dd, J = 2.3 Hz, J = 8.6 Hz), 6.63 (1H, d, J = 8.6 Hz), 4.92 (2H, s), 3.89 (3H, s), 2.57 (3H, s), 2.08 (4H, q, J = 7.3 Hz), 1.27 (9H, s), 0.63 (6H, t, J = 7.3 Hz).

ES (+) MS m/z: 462.4 [M+NH4].

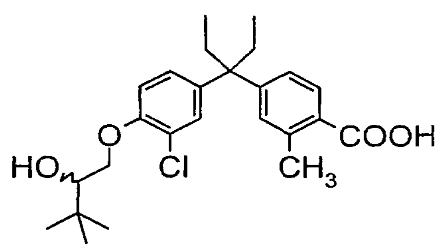
FAB (+) MS m/z [M+H]: 445.2; calc. m/z 445.1.

E. Racemic 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carbomethoxy)phenyl]pentane.



Using a procedure analogous to Example 35G, 3'-[3-chloro-4-(2-oxo-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carbomethoxy)phenyl]pentane was reduced by NaBH4 to provide the title compound as a colorless oil (735 mg, 98%).
H-NMR (300 mHz, CDCl3): δ 7.89 (1H, d, J = 8.8 Hz), 7.13 (1H, d, J = 1.78 Hz), 7.00 (2H, m), 6.93 (1H, dd, J = 2.2 Hz, J = 8.8 Hz), 6.80 (1H, d, J = 8.8 Hz), (4.17 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.86 (1H, m), 3.85 (3H, s), 3.74 (1H, m), 2.60, (1H, d, J = 3.0 Hz), 2.54 (3H, s), 2.06 (4H, q, J = 7.3 Hz), 1.01 (9H, s), 0.61 (6H, t, J = 7.3 Hz).
FAB (+) MS m/z [M+H]: 447.1; calc m/z 447.2.
IR (CHCl3): 1717 cm^{-1}

F. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carboxy)phenyl]pentane.



Using a procedure analogous to Example 35 H&I, racemic 3'-[3-chloro-4-(2-hydroxy-3.3-dimethylbutoxy)phenyl]-3'-[3-methyl-4-(carbomethoxy)-phenyl]pentane was saponified by aqueous NaOH in EtOH to form the Na salt corresponding to the desired compound. After removal of the EtOH under reduced pressure, the residue containing the Na salt was dissolved in water and acidified in a manner analogous to the procedure of Example CDJ-3 to provide the title compound as a white solid (470 mg, 97%).

H-NMR (300 mHz, DMSO): δ 7.72 (1H, d, J = 8.0 Hz), 7.00 to 7.10 (5H, m), 4.84 (1H, d, J = 5.6 Hz), 4.09 (1H, dd, J = 2.8 Hz, J = 10.4 Hz), 3.85 (1H, dd, J = 7.0 Hz, J = 10.4 Hz), 3.45 (1H, m), 2.47 (3H, s), 2.06 (4H, q, J = 7.3 Hz), 0.91 (9H, s), 0.55 (6H, t, J = 7.3 Hz).

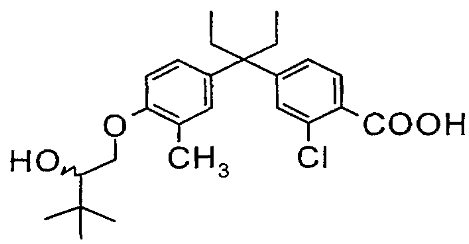
ES (+) MS m/z 450.2 [M+NH4], 455.2 [M+Na].

ES (-) MS m/z 431.1 [M-1].

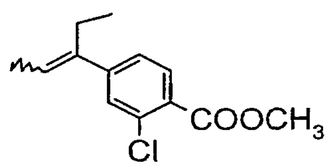
IR (CHCl3): 1689 cm^{-1}.

Example 39

Preparation of Racemic 3'-[3-methyl-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane.



A. [E,Z]-3-[3-Chloro-4-carbomethoxyphenyl)-3-pentene.



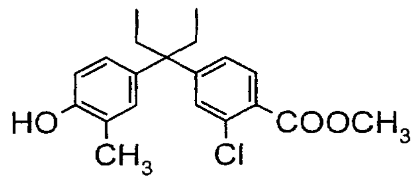
Using a procedure similar to Example 35F, a mixture of [E,Z]-3-[3-chloro-4-(trifluoromethylsulfonyloxy)phenyl)-3-pentene, MeOH, dppb, DMSO (instead of DMF), Et3N, and Pd(OAc)2 under an atmosphere of CO at 80 °C for 4 h are reacted to provide the title compound as a colorless liquid in a [E:Z] ratio of 9:1 (1.99 g, 92%).

H-NMR (300 mHz, CDCl3): δ 7.06-7.85 (3H, m), 5.85 (0.9H, q, J = 6.9 Hz), 5.60 (0.1H, q, J = 6.9 Hz), 3.94 (0.3H, s), 3.93 (2.7H, s), 2.50 (1.8H, q, J = 7.6 Hz), 2.32 (0.2H, q, J = 7.6 Hz), 1.82 (2.7H, d, J = 7.6 Hz), 1.53 (0.3H, d, J = 7.6 Hz), 0.97 (2.7H, t, J = 7.6 Hz), 0.94 (0.3H, t, J = 7.6 Hz).

IR (CHCl3): 1726 cm^{-1}

ES GC MS m/z 238.1, M+; Calc. C13H15ClO2 m/z 238.1

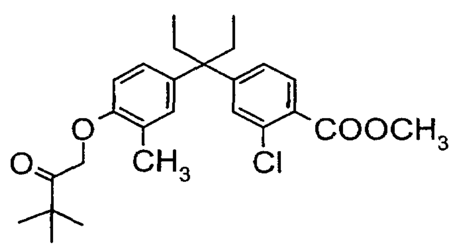
B. 3'-(4-hydroxy-3-methylphenyl)-3'-[3-chloro-4-carbomethoxyphenyl]pentane.



Using a procedure analogous to Example 35D, [E,Z]-3-[3-chloro-4-carbomethoxyphenyl)-3-pentene and o-cresol are reacted at RT overnight to give the title compound as a thick, pale yellow oil (3.54g, 99%).

H-NMR (300 mHz, CDCl3): δ 7.74 (1H, d, J = 8.2 Hz), 7.29 (1H, d, J= 1.7 Hz), 7.08 (1H, dd, J = 1.7 Hz, J = 8.2 Hz), 6.81 (2H, m), 6.63 (1H, d, J = 8.9 Hz), 3.91 (3H, s), 2.20 (3H, s), 2.09 (4H, q, J = 7.3 Hz), 1.27 (9H, s), 0.70 (6H, t, J = 7.3 Hz).
ES (+) MS m/z 347.1 [M+1].
IR (CHCl3): 1725 cm^{-1}.

C. 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-methyl-phenyl]-3'-(3-chloro-4-carbomethoxyphenyl)-pentane.

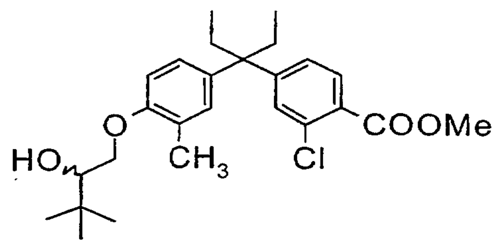


Using a procedure analogous to Example 35C, 3'-(4-hydroxy-3-methylphenyl)-3'-[3-chloro-4-carbomethoxyphenyl]pentane, 1-chloropinacolone, anhydrous KI, and K2CO3 are reacted in acetonitrile to give the title compound as a clear colorless oil (3.46g, 90%).

H-NMR (300 mHz, CDCl3): δ 7.70 (1H, d, J = 8.2 Hz), 7.28 (1H, d, J= 1.8 Hz), 7.07 (1H, dd, J =1.8, J =8.2), 6.858 – 6.87 (2H, m), 6.50 (1H, d, J = 9.2 Hz), 4.84 (2H, s), 3.91 (3H, s), 2.23 (3H, s), 2.05 (4H, q, J = 7.3 Hz), 1.53 (9H, s), 0.61 (6H, t, J = 7.3 Hz).
FAB(+) MS m/z [M+H]: 445.2 Calc. m/z 445.2.

IR (CHCl3): 1725 cm^{-1}.

D. Racemic 3'-[3-methyl-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carbomethoxyoxyphenyl)pentane.



Using a procedure analogous to Example 35G, 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-methyl-phenyl]-3'-(3-chloro-4-carbomethoxyphenyl)-pentane was reduced by NaBH4 to provide the title compound as a colorless oil (2.75 g, 91%).
H-NMR (300 mHz, CDCl3): δ 7.75 (1H, d, J = 8.8 Hz), 7.27 (1H, d, J = 1.8 Hz), 7.16 (1H, d, J =2.0 Hz), 7.07 (1H, dd, J = 1.8 Hz, J = 8.8 Hz), 6.94 (1H, dd, J = 2.0 Hz, J = 8.8 Hz), 6.83 (1H, d, J = 8.8 Hz), 4.18 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.92 (3H, s), 3.89 (1H, m), 3.74 (1H, m), 2.60, (1H, broad s), 2.06 (4H, q, J = 7.3 Hz), 1.04 (9H, s), 0.63 (6H, t, J = 7.3 Hz).
FAB(+) MS m/z [M+H]: 447.3; calc. m/z 447.2
IR (CHCl3): 1733 cm^{-1}

E. Racemic 3'-[3-methyl-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane..

Using a procedure analogous to Example 35H, racemic 3'-[3-methyl-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carbomethoxyoxyphenyl)pentane was saponified by aqueous NaOH in EtOH to form the Na salt corresponding to the desired compound. After removal of the EtOH under reduced pressure, the residue containing the Na salt was dissolved in water and acidified in a manner analogous to the procedure of Example 39I to provide the title compound as a white solid (1.84 g, 93%).
H-NMR (300 mHz, DMSO): δ 7.69 (1H, d, J = 8.0 Hz), 7.10 to 7.20 (2H, m), 6.80 to 6.95 (3H, m),4.78 (1H, d, J = 5.6 Hz), 4.02 (1H, dd, J = 2.8 Hz, J = 10.4 Hz), 3.76 (1H, dd, J =

7.0 Hz, J = 10.4 Hz), 3.44 (1H, m), 2.10 (3H, s), 2.04 (4H, q, J = 7.3 Hz), 0.93 (9H, s), 0.56 (6H, t, J = 7.3 Hz).

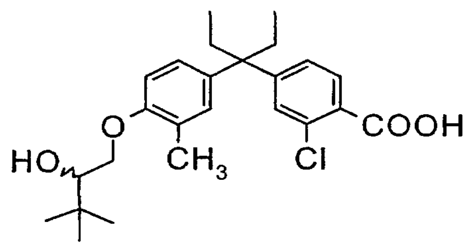
ES (+) MS m/z 433.2 [M+H], 450.1 [M+NH4], 455.1 [M+Na].

ES (-) MS m/z 431.2 [M-H].

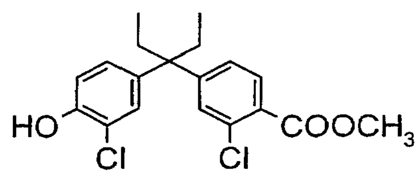
IR (CHCl3): 1701 cm^{-1}.

Example 40

Preparation of racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane.



A. 3'-(4-hydroxy-3-chlorophenyl)-3'-(3-chloro-4-carbomethoxy-phenyl)pentane.



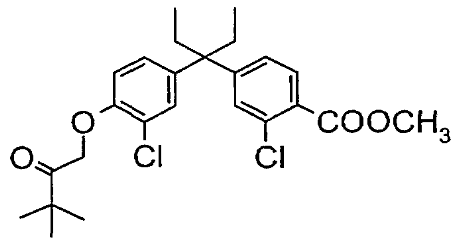
Using a procedure analogous to Example 35D, [E,Z]-3-[3-chloro-4-carbomethoxyphenyl]-3-pentene and o-chlorophenol are reacted (initially at RT overnight, then at 70 °C for 20 h, and finally at 90 °C overnight) to give the title compound as an oil (886 mg, 58%).

H-NMR (300 mHz, CDCl3): 6.90 to 7.76 (6H, m), 5.45 (1H, s), 3.93 (3H, s), 2.06 (4H, q, J = 7.3 Hz), 0.64 (6H, t, J =7.3 Hz).

ES (+) MS m/z 367.0 [M+H].

IR (CHCl3): 1726 cm^{-1}

B. 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-chlorophenyl]-3'-(3-chloro-4-carbomethoxyphenyl)-pentane.

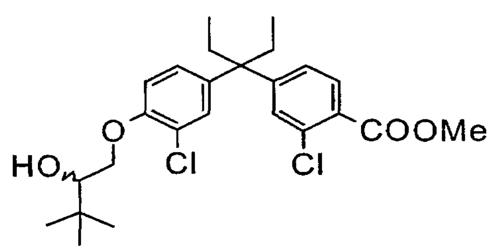


Using a procedure analogous to Example 35C, 3'-(4-hydroxy-3-chlorophenyl)-3'-(3-chloro-4-carbomethoxy-phenyl)pentane, 1-chloropinacolone, anhydrous KI, and K2CO3 are reacted in acetonitrile to give the title compound as a clear, nearly colorless oil (919 mg, 89%).

H-NMR (300 mHz, CDCl3): δ 7.72 (1H, d, J = 8.2 Hz), 7.26 (1H, m), 7.17 (1H, d, J =2.3, 7.06 (1H, dd, J = 1.8 Hz, J = 8.2 Hz), 6.90 (1H, dd, J = 8.7 Hz, J = 2.3 Hz), 4.91 (2H, s), 3.92 (3H, s), 2.05 (4H, q, J = 7.3 Hz), 1.26 (9H, s), 0.62 (6H, t, J = 7.3 Hz).

ES (+) MS m/z 465.1 [M+H], 482.1 [M+NH4].

C. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carbomethoxyphenyl)pentane.



Using a procedure analogous to Example 35G, 3'-[4-(2-oxo-3,3-trimethylbutoxy)-3-chlorophenyl]-3'-(3-chloro-4-carbomethoxyphenyl)-pentane was reduced by NaBH4 to provide the title compound as a colorless oil (738 mg, 98%).

H-NMR (300 mHz, CDCl3): δ 7.89 (1H, d, J = 8.8 Hz), 7.13 (1H, d, J = 1.78 Hz), 7.00 (2H, m), 6.93 (1H, dd, J = 2.2 Hz, J = 8.8 Hz), 6.80 (1H, d, J = 8.8 Hz), (4.17 (1H, dd, J = 2.6 Hz, J = 9.0 Hz), 3.86 (1H, m), 3.85 (3H, s), 3.74 (1H, m), 2.60, (1H, d, J = 3.0 Hz), 2.06 (4H, q, J = 7.3 Hz), 1.01 (9H, s), 0.61 (6H, t, J = 7.3 Hz).

ES (+) MS m/z 489.2 (M+Na).

IR (CHCl3): 1717 cm^{-1}

D. Racemic 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane.

Using a procedure analogous to Example 35H, racemic 3'-[3-methyl-4-(2-hydroxy-3,3-dimethylbutoxy)phenyl]-3'-(3-chloro-4-carbomethoxy-phenyl)pentane was saponified by aqueous NaOH in EtOH to form the Na salt corresponding to the desired compound. After removal of the EtOH under reduced pressure, the residue containing the Na salt was dissolved in water and acidified in a manner analogous to the procedure of Example 39I to provide the title compound as a white solid (517 mg, 94%).

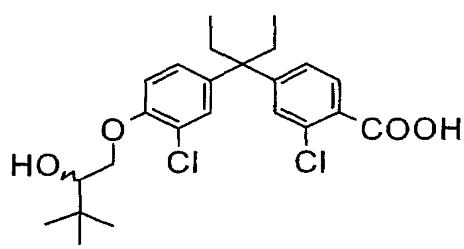
H-NMR (300 mHz, DMSO): δ 7.74 (1H, d, J = 8.0 Hz), 7.04 to 7.30 (5H, m), 4.88 (1H, d, J = 5.6 Hz), 4.14 (1H, dd, J = 2.8 Hz, J = 10.4 Hz), 3.89 (1H, dd, J = 7.0 Hz, J = 10.4 Hz), 3.49 (1H, m), 2.04 (4H, q, J = 7.3 Hz), 0.95 (9H, s), 0.58 (6H, t, J = 7.3 Hz).

ES (+) MS m/z 475.2 [M+Na].

IR (CHCl3): 1701 cm^{-1}.

Example 41 and Example 42

Separation of optical isomers of 3'-[3-chloro-4-(2-hydroxy-3,3-dimethyl-butoxy)phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane.



(isomer 1)

(isomer 2)

A racemic mixture 3'-[3-chloro-4-(2-hydroxy-3,3-dimethylbutoxy)-phenyl]-3'-(3-chloro-4-carboxyphenyl)pentane. (490 mg) is chromatographed with a ChiralpakAD column to give enantiomer 1, Example 41 (192 mg, 39%) and enantiomer 2, Example 42 (185 mg, 38%).

Enantiomer 1, Example 41

HPLC: Chiralpak AD (4.6 X 250 mm); 3:2 heptane: isopropyl alcohol with 0.1% TFA; 1.0 mL/m (flow rate); rt = 7.8 m; 270 nm; ee 99.9% by HPLC.

H-NMR (300 mHz, DMSO): δ 7.74 (1H, d, J = 8.0 Hz), 7.04 to 7.30 (5H, m), 4.88 (1H, d, J = 5.6 Hz), 4.14 (1H, dd, J = 2.8 Hz, J = 10.4 Hz), 3.89 (1H, dd, J = 7.0 Hz, J = 10.4 Hz), 3.49 (1H, m), 2.04 (4H, q, J = 7.3 Hz), 0.95 (9H, s), 0.58 (6H, t, J = 7.3 Hz).

ES (+) MS m/z 475.2 [M+Na].

Enantiomer 2, Example 42

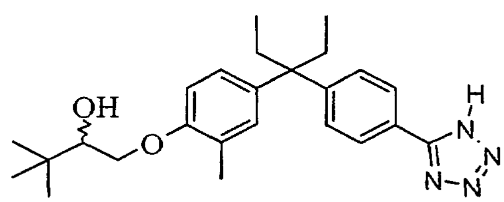
HPLC: Chiralpak AD (4.6 X 250 mm); 3:2 heptane: isopropyl alcohol with 0.1% TFA; 1.0 mL/m (flow rate); rt = 10.6 m; 270 nm; ee 99.5% by HPLC.

H-NMR (300 mHz, DMSO): δ 7.74 (1H, d, J = 8.0 Hz), 7.04 to 7.30 (5H, m), 4.88 (1H, d, J = 5.6 Hz), 4.14 (1H, dd, J = 2.8 Hz, J = 10.4 Hz), 3.89 (1H, dd, J = 7.0 Hz, J = 10.4 Hz), 3.49 (1H, m), 2.04 (4H, q, J = 7.3 Hz), 0.95 (9H, s), 0.58 (6H, t, J = 7.3 Hz).

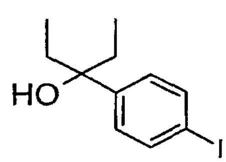
ES (+) MS m/z 475.1 [M+Na].

Example 43

Preparation of racemic 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-ol.



A. 3'-(4-Iodophenyl)-3'-pentanol.

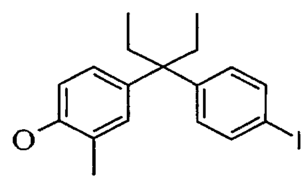


To ethyl, p-iodobenzoate (11.04 g, 40 mmol) in diethylether (100 mL) at –20° C. under nitrogen is added 1M ethylmagnesium bromide (91 mL, 91 mmol) dropwise with mechanical stirring, and the mixture is allowed to come to R.T. and stirred over

night. The mixture is quenched with satd. sodium bicarbonate and triturated with diethylether six times. The organic layers are combined; washed with water; dried over anhydrous sodium sulfate; and evaporated under vacuum to give the title compound as an oil (10.4 g, 90%) which is used as is.

^{1}H NMR (400 mHz, $CDCl_3$), δ 7.64 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 1.74-1.85 (m, 4H), 0.75 (t, J = 7.4 Hz, 6h).

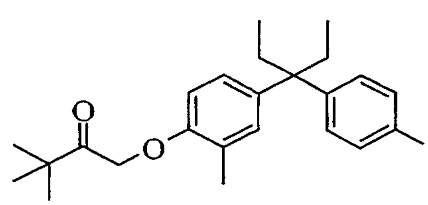
B. 1-{4-[1-Ethyl-1-(4-iodophenyl)-propyl]}-2-methyl-phenol.



To 3'-(4-iodophenyl)-3'-pentanol (10.4 g, 36 mmol) and o-cresol (15.5 g, 143 mmol) in methylene chloride (5 mL) is added borontrifluoride etherate (0.96 mL, 7.2 mmol), and the mixture is allowed to stir at room temperature overnight. The mixture is quenched with satd. sodium bicarbonate, and extracted into diethylether. The organic phase is washed with water; dried over anhydrous sodium sulfate; and evaporated under vacuum. The residue is vacuum distilled (0.5 mm) to 80 °C. to remove excess o-cresol, and the residue is partitioned between diethylether and water. The organic layer is dried over anhydrous sodium sulfate, and evaporated under vacuum to give the title compound as an oil (13 g, 95%) which is used as is.

^{1}H NMR (400 mHz, $CDCl_3$), δ 7.53 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.84 (s, 1H), 6.83 (d. J = 8.9 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 4.50 (s, 1H), 2.20 (s, 3H), 2.01 (q, J = 7.2 Hz, 4H), 0.60 (t, J = 7.2 Hz, 6H).

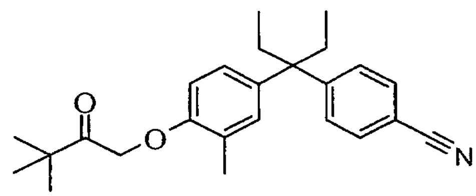
C. 1-{4-[1-Ethyl-1-(4-iodophenyl)-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one.



In a procedure analogous to Example 35C, 1-{4-[1-Ethyl-1-(4-iodophenyl)-propyl]}-2-methyl-phenol (13 g, 34 mmol) gave the title compound as an oil (13.9 g, 85%) which is used as is.

^{1}H NMR (400 mHz, $CDCl_3$), δ 7.53 (d, J = 8.4 hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.87 (s, 1H), 6.86 (d, J = 8.8 hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.83 (s, 2H), 2.23 (s, 3H), 2.01 (q, J = 7.2 Hz, 4H), 1.25 (s, 9H).

D. 4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzonitrile.

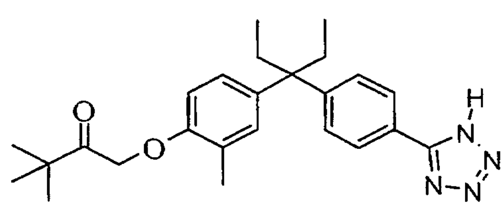


To a mixture of 1-{4-[1-ethyl-1-(4-iodo-phenyl)-propyl]-2-methyl-phenoxy}-3,3-dimethyl-butan-2-one (3.0 g 6.27 mmol) and DMF (30 mL) is added $Zn(CN)_2$ (0.44 g, 3.76 mmol), $Pd_2(dba)_3$ (0.29 g, 0.31 mmol), and DPPF (0.42 g, 0.75 mmol). The solution is heated at 100 °C overnight, diluted with Et_2O (200 mL), washed with 4:1:4 sat NH_4Cl:Conc. NH_4OH:water (100 mL), water (100 mL), brine (100 mL), dried $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-2-% EtOAc gradient) to furnish the title compound (1.1 g, 2.91 mmol, 46%).

^{1}H NMR ($CDCl_3$), δ 0.52-0.63 (m, 6H), 1.26 (s, 9H), 2.03-2.10 (m, 4H), 2.24 (s, 3H), 4.85 (s, 2H), 6.50 (d, J = 9.4 Hz, 1H), 6.82-6.86 (m, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.9 Hz, 2H).

LC/MS (m/z): calcd. for $C_{25}H_{31}NO_2$ $(M+H)^+$: 378.6; found: 395.3.

E 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one.



To a mixture of 4-{1-[4-(3,3-dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-1-ethyl-propyl}-benzonitrile (0.50 g, 1.32 mmol), and DMF (5 mL) is added NaN_3 (0.26 g, 3.95 mmol) and $Et_3N{\bullet}HCl$ (0.54 g, 3.95 mmol). The slurry is heated at 110 °C overnight. The slurry is diluted with EtOAc (50 mL), washed with 1M HCl (40 mL) water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (20%- 40% [89% EtOAc: 10% MeOH: 1% AcOH] gradient) to furnish the title compound (0.37g, 0.88 mmol, 66%).

^1H NMR ($CDCl_3$), δ 0.57-0.62 (m, 6H), 1.27 (s, 9H), 2.02-2.11 (m, 4H), 2.17 (s, 3H), 4.87 (s, 2H), 6.50 (d, J = 9.4 Hz, 1H), 6.82-6.88 (m, 2H), 7.22-7.28 (m, 3H), 7.94 (d, J = 7.9 Hz, 2H).

LC/MS (m/z): calcd. for $C_{25}H_{32}N_4O_2$ $(M+H)^+$: 421.7; found: 421.2.

F. 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-ol.

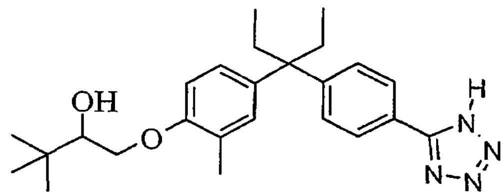
To a mixture of 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one (0.37 g, 0.88 mmol) and EtOH (5 mL) was added $NaBH_4$ (0.037 g, 0.97 mmol) and the solution stirred for 1 hour. The solids were removed by filtration and the solution concentrated. The residue was purified by ISCO (10- 30 [89% EtOAc:10% MeOH: 1% AcOH] gradient) to furnish the title compound (0.32 g, 0.76 mmol, 86%).

^1H NMR ($CDCl_3$), δ 0.59-0.64 (m, 6H), 1.02 (s, 9H), 2.05-2.12 (m, 4H), 2.13 (s, 3H), 3.75 (dd, J = 2.8, 8.8 Hz, 1H), 3.89 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.8, 8.8 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 2.2, 8.7 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H).

LC/MS (m/z): calcd. for $C_{25}H_{34}N_4O_2$ $(M+H)^+$: 423.7; found: 423.2.

Example 44 and Example 45

Separation of enantiomers of 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-ol.



enantiomer 1

enantiomer 2

A racemic mixture of 1-(4-{1-Ethyl-1-[4-(1H-tetrazol-5-yl)-phenyl]-propyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-ol (0.32 g) is chromatographed (CHIRALPAK ADH column, 0.1% TFA, 20% *i*-PrOH/Hept) to give enantiomer 1, (0.168 g, 0.40 mmol, 45 %) and enantiomer 2, (0.150 g, 0.35 mmol, 41 %).

Example 44, enantiomer 1

Rt = 7.7 m

^{1}H NMR ($CDCl_3$), δ 0.57-0.67 (m, 6H), 1.02 (s, 9H), 2.05-2.12 (m, 4H), 2.14 (s, 3H), 3.74 (dd, J = 2.2, 8.8 Hz, 1H), 3.89 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.2, 8.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.86 (s, 1H), 6.93 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H). LC/MS (m/z): calcd. for $C_{25}H_{34}N_4O_2$ $(M+H)^+$: 423.7; found: 423.3.

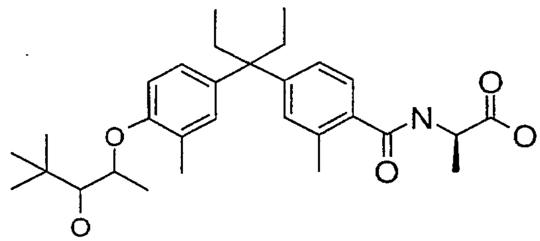
Example 45, enantiomer 2

Rt = 11.6 m

^{1}H NMR ($CDCl_3$), δ 0.59-0.66 (m, 6H), 1.01 (s, 9H), 2.05-2.15 (m, 4H), 2.16 (s, 3H), 3.71 (dd, J = 2.5, 8.7 Hz, 1H), 3.87 (t, J = 9.0 Hz, 1H), 4.09 (dd, J = 2.5, 9.0 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 1.7 Hz, 1H), 6.95 (dd, J = 2.2, 8.5 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H). LC/MS (m/z): calcd. for $C_{25}H_{34}N_4O_2$ $(M+H)^+$: 423.7; found: 423.3.

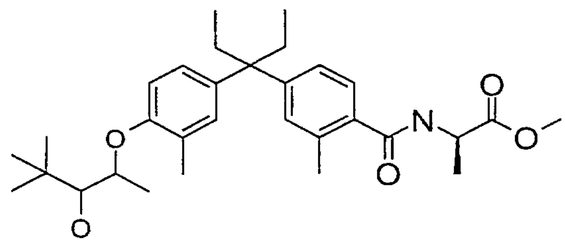
Example 46

Preparation of epimer 1 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid



(Epimer 1, *D*-)

A. Preparation of epimer 1 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester.



(Epimer 1, *D*-)

Using a procedure analogous to Example 5, isomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.55 g, 1.29 mmol). (D)-alananine methyl ester hydrochloride (198 mg, 1.42 mmol), EDCI (276 mg, 1.44 mmol), and 1-hydroxybenzotriazole hydrate (195 mg, 1.44 mmol) furnish the title compound (0.42 g, 0.82 mmol, 63%).

^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.3 Hz, 6H), 0.97 (S, 9H), 1.35 (d, J = 6.3 Hz, 3H), 1.51 (d, J = 7.5 Hz, 3H), 2.06 (q, J = 7.3 Hz, 4H), 2.14 (s, 3H), 2.43 (s, 3H), 3.18 (bs, 1H), 3.79 (s, 3H), 4.58 (q, J = 6.3 Hz, 1H), 4.79 (m, 1H), 6.32 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.84-7.05 (m, 4H), 7.30 (d, J = 8.3 Hz, 1H).

ES-MS (m/z): calcd. for $C_{31}H_{46}NO_5$ $(M+H)^+$: 511.7; found: 512.3.

B. Preparation of epimer 1 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.

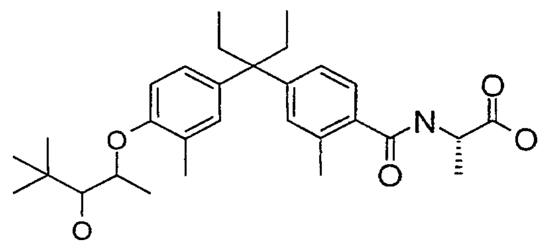
Using a procedure analogous to Example 2, epimer 1 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester (0.42 g, 0.82 mmol) and LiOH give the title compound (0.41 g, 0.82 mmol, 100%).

^1H NMR ($CDCl_3$), δ 0.62 (t, J = 7.5 Hz, 6H), 0.97 (S, 9H), 1.36 (d, J = 6.2 Hz, 3H), 1.57 (d, J = 7.0 Hz, 3H), 2.06 (q, J = 7.5 Hz, 4H), 2.14 (s, 3H), 2.44 (s, 3H), 3.19 (d, J = 0.9 Hz, 1H), 4.58 (dq, J = 6.2, 0.9 Hz, 1H), 4.74-4.82 (m, 1H), 6.28 (d, J = 7.0 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.84-7.06 (m, 4H), 7.31 (d, J = 7.9 Hz, 1H). ES-MS (m/z): calcd. for $C_{31}H_{46}NO_5$ $(M+H)^+$: 511.7; found: 512.3.).

ES-MS (m/z): calcd for $C_{30}H_{42}NO_5$ $(M-H)^-$: 496.7; found: 496.3.

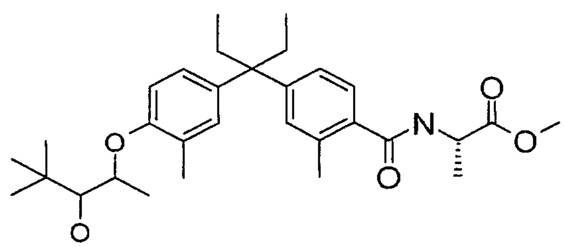
Example 47

Preparation of epimer 1 of (*L*)-2-(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.



(Epimer-1, L-)

A. Preparation of epimer 1 of (*L*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester.



(Epimer-1, L-)

Using the procedure analogous to Example 46A, isomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.55 g, 1.29 mmol) and (L)-alananine methyl ester hydrochloride (198 mg, 1.42 mmol) furnish the title compound (0.56 g, 1.09 mmol, 85%).

^1H NMR ($CDCl_3$), δ 0.62 (t, J = 7.2 Hz, 6H), 0.97 (S, 9H), 1.36 (d, J = 6.1 Hz, 3H), 1.51 (d, J = 7.4 Hz, 3H), 2.06 (q, J = 7.2 Hz, 4H), 2.15 (s, 3H), 2.43 (s, 3H), 3.18 (bs, 1H), 3.79 (s, 3H), 4.58 (dq, J = 6.1, 0.9 Hz, 1H), 4.79 (m, 1H), 6.32 (d, J = 7.3 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 6.84-7.05 (m, 4H), 7.30 (d, J = 8.3 Hz, 1H).

ES-MS (m/z): calcd. for $C_{31}H_{46}NO_5$ $(M+H)^+$: 511.7; found: 512.3.

B. Preparation of epimer 1 of (*L*)-2-(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.

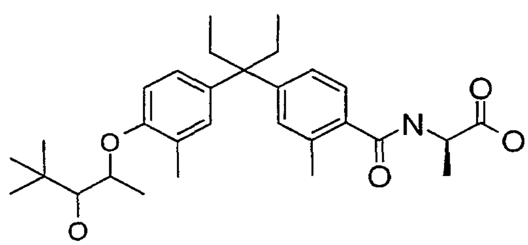
Using a procedure analogous to Example 46B, epimer 1 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester (0.56 g, 1.09 mmol) gives the title compound (0.54 g, 1.09 mmol, 100%).

^{1}H NMR ($CDCl_3$), δ 0.62 (t, J = 7.0 Hz, 6H), 0.97 (S, 9H), 1.36 (d, J = 6.1 Hz, 3H), 1.57 (d, J = 7.4 Hz, 3H), 2.06 (q, J = 7.0 Hz, 4H), 2.14 (s, 3H), 2.44 (s, 3H), 3.19 (d, J = 1.3 Hz, 1H), 4.59 (q, J = 6.1, Hz, 1H), 4.74-4.82 (m, 1H), 6.29 (d, J = 7.0 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 6.84-7.07 (m, 4H), 7.31 (d, J = 8.4 Hz, 1H).

ES-MS (m/z): calcd for $C_{30}H_{42}NO_5$ $(M-H)^-$: 496.7; found: 496.3.

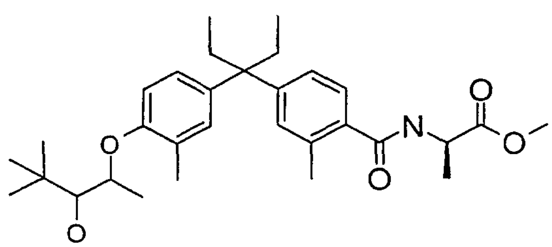
Example 48

Preparation of epimer 2 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.



(*Epimer-2, D-*)

A. Preparation of epimer 2 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester.



(*Epimer-2, D-*)

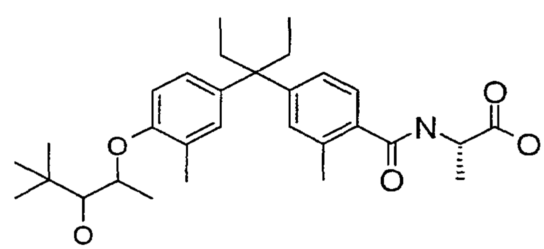
Using the procedure analogous to Example 46A, isomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.50 g, 1.17 mmol) and (D)-alananine methyl ester hydrochloride (180 mg, 1.29 mmol) furnish the title compound (0.47 g, 0.92 mmol, 79%). ^{1}H NMR) & ES-MS (m/z): identical to that of Example 47A.

B. Preparation of epimer 2 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.

Using a procedure analogous to Example 46B, from epimer 2 of (*D*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester (0.47 g, 0.92 mmol) to give the title compound (0.39 g, 0.79 mmol, 86%). ^{1}H NMR & ES-MS : identical to that of Example 47B.

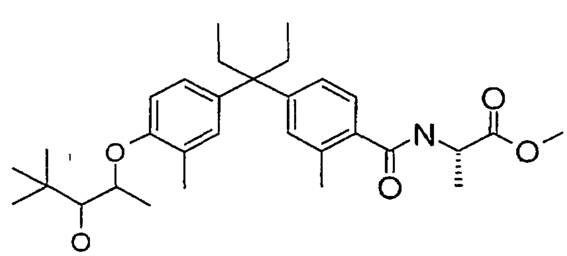
Example 49

Preparation of epimer 2 of (*L*)-2-(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.



(*Epimer-2, L-*)

A. Preparation of epimer 2 of (*L*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester.



(*Epimer-2, L-*)

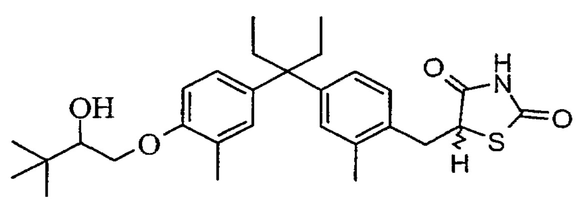
Using the procedure analogous to Example 46A, isomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.50 g, 1.17 mmol) and (L)-alananine methyl ester hydrochloride (180 mg, 1.29 mmol) furnish the title compound (0.47 g, 0.92 mmol, 79%). ^{1}H NMR) & ES-MS (m/z): identical to that of Example 46A.

B. Preparation of epimer 2 of (*L*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid.

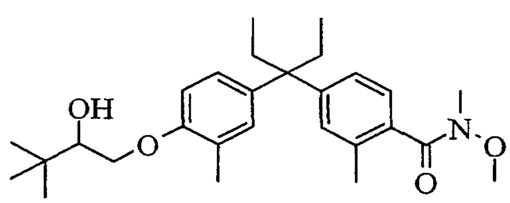
Using a procedure analogous to Example 24B, epimer 2 of (*L*)-2-(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoylamino)-propionic acid methyl ester (0.47 g, 0.92 mmol) give the title compound (0.44 g, 0.88 mmol, 96%). ^{1}H NMR & ES-MS: identical to that of Example 46B.

Example 50

Preparation of enantiomer 1 of 5-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyl)-thiazolidine-2,4-dione.



A. Enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-N-methoxy-2,N-dimethyl-benzamide.

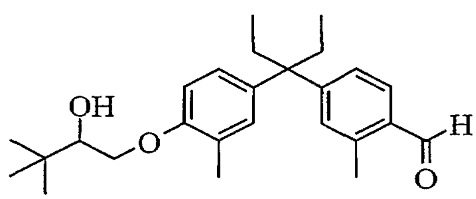


To a mixture of enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (1.11 g, 2.69 mmol) and DMF (5 mL) is added hydroxylamine hydrochloride (0.29 g, 2.96 mmol), EDCI (0.57 g, 2.96 mmol), HOBt (0.40 g, 2.96 mmol), and NEt_3 (1.65 mL, 11.84 mmol). The mixture is

stirred at ambient temperature overnight, diluted with EtOAc (40 mL), washed with 1M HCl (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by ISCO (10%-40% EtOAc gradient) to furnish the title compound (1.0 g, 2.19 mmol, 81%).

^{1}H NMR ($CDCl_3$), δ 0.57-0.64 (m, 6H), 1.02 (s, 9H), 2.02-2.10 (m, 4H), 2.17 (s, 3H), 2.29 (s, 3H), 3.28 (bs, 3H), 3.53 (bs, 1H), 3.71 (dd, J = 2.7, 8.8 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.7, 8.8 Hz, 1H), 6.70 (d, J = 8.6 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 6.94 (dd, J = 2.2, 8.1 Hz, 1H), 6.97-7.02 (m, 3H), 7.14 (d, J = 8.4 Hz, 1H). LC/MS (m/z): calcd. for $C_{28}H_{41}NO_4$ $(M+H)^+$: 456.7; found: 456.2.

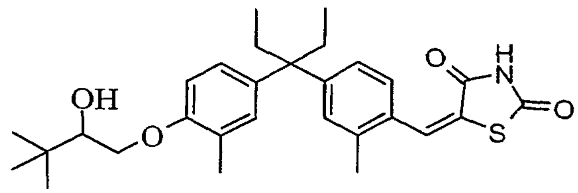
B. Enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzaldehyde.



To a mixture of enantiomer 1 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-N-methoxy-2,N-dimethyl-benzamide (1.0 g, 2.42 mmol) and THF (10 mL) is added 1M in THF LAH (2.5 mL, 2.55 mmol) with cooling. THF (5 mL) was added and the solution stirred for 1 hour. The solution is diluted with Et_2O (100 mL) and washed with 1M HCl (50 mL). The aqueous phase is extracted with Et_2O (50 mL). The combined organic layers are washed with 1M HCl (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.64 g, 1.61 mmol, 67%).

^{1}H NMR ($CDCl_3$), δ 0.59-0.66 (m, 6H), 1.02 (s, 9H), 2.05-2.15 (m, 4H), 2.18 (s, 3H), 2.62 (s, 3H), 3.71 (dd, J = 1.9, 9.1 Hz, 1H), 3.86 (t, J = 9.1 Hz, 1H), 4.10 (dd, J = 1.9, 9.1 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 6.87 (s, 1H), 6.93 (d, J = 8.7 Hz, 1H), 7.06 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H) 7.67 (dd, J = 1.7, 8.0, 1H), 10.20 (s, 1H).
LC/MS (m/z): calcd. for $C_{26}H_{36}O_3$ $(M+H)^+$: 397.7.; found: N/A.

C. Enantiomer 1 of 5-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzylidene)-thiazolidine-2,4-dione.



To a mixture of enantiomer 1 of 4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzaldehyde (0.64 g, 1.61 mmol) and toluene (20 mL) is added 90 % 2,4-thiazolidinedione (0.25 g, 1.94 mmol), and piperdine acetate (0.04 g, 0.24 mmol). The solution is heated to a reflux overnight and the water removed by a Dean-Stark trap. The solution is diluted with EtOAc (60 mL), washed with water (50 mL), saturated $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO (20% –50% EtOAc gradient) to furnish the title compound (0.75 g, 1.51 mmol, 94%).

^{1}H NMR ($CDCl_3$), δ 0.60-0.67 (m, 6H), 1.03 (s, 9H), 2.04-2.13 (m, 4H), 2.19 (s, 3H), 2.42 (s, 3H), 2.50 (d, J = 2.0 Hz, 1H), 3.72 (d, J = 8.8 Hz, 1H), 3.86 (t, J = 8.9 Hz, 1H), 4.10 (dd, J = 2.7, 9.4 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 1.7 Hz, 1H), 6.94 (dd, J = 2.3, 8.7 Hz, 1H), 7.08 (s, 1H), 7.11 (dd, J = 1.8, 8.4 Hz, 1H), 7.33 (d, J = 8.4, 1H), 8.06 (s, 1H), 8.97 (bs, 1H).

LC/MS (m/z): calcd. for $C_{29}H_{37}NO_4S$ $(M+H)^+$: 494.5; found: 494.2.

D. Enantiomer 1 of 5-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyl)-thiazolidine-2,4-dione.

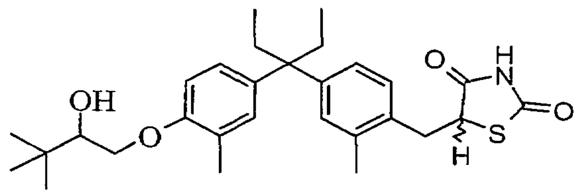
To a mixture of enantiomer 1 of 5-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzylidene)-thiazolidine-2,4-dione (0.35 g, 0.71 mmol) and MeOH (10 mL) is added Mg (0.17 g, 7.1 mmol). The solution is heated at a reflux for 4 hours. The solution is filtered thru celite®, rinsed with MeOH (2 mL), and the solution concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient) to furnish the title compound (0.13 g, 0.26 mmol, 37%).

^{1}H NMR ($CDCl_3$), δ 0.57-0.65 (m, 6H), 1.02 (s, 9H), 2.01-2.10 (m, 4H), 2.19 (s, 3H), 2.31 (s, 3H), 2.50 (d, J = 2.6 Hz, 1H), 2.97-3.06 (m, 1H), 3.65 (dd, J = 3.8, 14.5 Hz, 1H), 3.69-3.75 (m, 1H), 3.87 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.7, 9.3 Hz, 1H), 4.52 (dd, J = 3.8, 11.2 Hz, 1H), 6.70 (dd, J = 2.3, 8.5 Hz, 1H), 6.87-7.04 (m, 5H), 8.56 (bs, 1H).

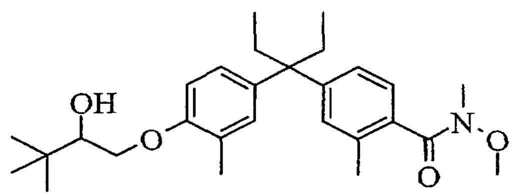
LC/MS (m/z): calcd. for $C_{29}H_{39}NO_4S$ $(M+H)^+$: 496.6; found: 496.2.

Example 51

Preparation of enantiomer 2 of 5-(4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyl)-thiazolidine-2,4-dione.



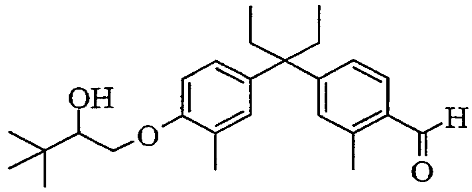
A. Enantiomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-N-methoxy-2,N-dimethyl-benzamide.



To mixture of enantiomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (0.70 g, 1.70 mmol) and DMF (5 mL) is added hydroxylamine hydrochloride (0.18 g, 1.87 mmol), EDCI (0.33 g, 1.87 mmol), HOBt (0.23 g, 1.87 mmol), and NEt_3 (0.95 mL, 6.79 mmol). The mixture is stirred at ambient temperature overnight, diluted with EtOAc (40 mL), washed with 1M HCl (40 mL), water (40 mL), brine (40 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.76 g, 2.19 mmol, 81%).

^1H NMR ($CDCl_3$), δ 0.57-0.64 (m, 6H), 1.02 (s, 9H), 2.01-2.10 (m, 4H), 2.17 (s, 3H), 2.28 (s, 3H), 3.28 (bs, 3H), 3.54 (bs, 1H), 3.71 (dd, J = 2.6, 8.8 Hz, 1H), 3.86 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.6, 8.8 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H), 6.94 (dd, J = 2.2, 8.6 Hz, 1H), 6.97-7.02 (m, 3H), 7.13 (d, J = 8.3 Hz, 1H). LC/MS (m/z): calcd. for $C_{28}H_{41}NO_4$ $(M+H)^+$: 456.7; found: 456.3.

B. Enantiomer 2 of 4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzaldehyde.

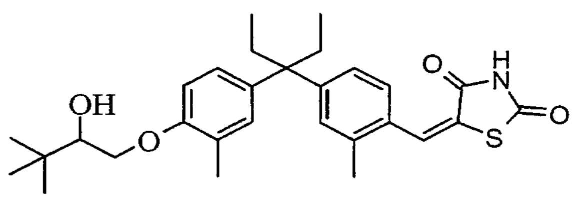


To a mixture of enantiomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-N-methoxy-2,N-dimethyl-benzamide (0.76 g, 1.75 mmol) and THF (20 mL) is added 1M LAH in THF (1.75mL, 1.75 mmol) with cooling, and the solution stirred for 1 hour. The solution is diluted with Et_2O (100 mL) and washed with 1M HCl (50 mL). The aqueous phase is extracted with Et_2O (50 mL). The combined organic layers are washed with 1M HCl (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to furnish the title compound (0.48 g, 1.21 mmol, 73%).

^{1}H NMR ($CDCl_3$), δ 0.60-0.65 (m, 6H), 1.02 (s, 9H), 2.07-2.14 (m, 4H), 2.18 (s, 3H), 2.62 (s, 3H), 3.58-3.74 (m, 1H), 3.87 (t, J = 8.9 Hz, 1H), 4.10 (dd, J = 2.6, 9.2 Hz, 1H), 6.72 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 2.5, 8.6, 1H), 7.06 (s, 1H), 7.17 (dd, J = 1.8, 8.2 Hz, 1H), 7.67 (d, J = 8.4, 1H), 10.20 (s, 1H).

LC/MS (m/z): calcd. for $C_{26}H_{36}O_3$ $(M+H)^+$: 397.7.; found: 397.3.

C. Enantiomer 2_ of 5-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzylidene)-thiazolidine-2,4-dione.



To a mixture of enantiomer 2 of 4-{1-ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzaldehyde (048 g, 1.21 mmol) and toluene (15 mL) is added 90 % 2,4-thiazolidinedione (0.19 g, 1.45 mmol), and piperdine acetate (0.03 g, 0.18 mmol). The solution is heated to a reflux overnight and the water removed by a Dean-Stark trap. The solution is diluted with EtOAc (60 mL), washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purified by ISCO (20% –40% EtOAc gradient) to furnish the title compound (0.50 g, 1.00 mmol, 83%).

^{1}H NMR ($CDCl_3$), δ 0.60-0.67 (m, 6H), 1.03 (s, 9H), 2.05-2.12 (m, 4H), 2.19 (s, 3H), 2.42 (s, 3H), 2.51 (d, J = 2.5 Hz, 1H), 3.70-3.75 (m, 1H), 3.88 (t, J = 8.8 Hz, 1H), 4.10 (dd, J = 2.7, 9.2 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.94 (dd, J = 2.2, 8.6 Hz, 1H), 7.08 (s, 1H), 7.11 (dd, J = 1.8, 8.0 Hz, 1H), 7.33 (d, J = 8.0, 1H), 8.06 (s, 1H), 9.02 (bs, 1H).

LC/MS (m/z): calcd. for $C_{29}H_{37}NO_4S$ $(M+H)^+$: 494.5; found: 494.2.

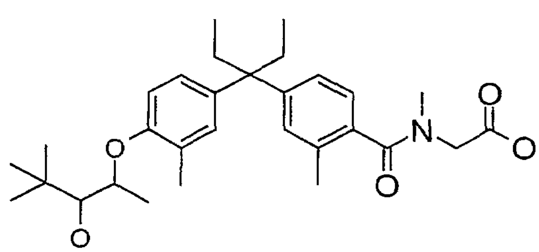
D. Enantiomer 2 of 5-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzyl)-thiazolidine-2,4-dione.

To a mixture of enantiomer 2 of 5-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzylidene)-thiazolidine-2,4-dione (example Rupp-7) (0.25 g, 0.50 mmol) and MeOH (10 mL) is added Mg (0.12 g, 5.04 mmol). The solution is heated at a reflux for 4 hours. The solution is filtered thru celite®, rinsed with MeOH (2 mL), and the solution concentrated. The residue is purified by ISCO (15%-30% EtOAc gradient) to furnish the title compound (0.084 g, 0.17 mmol, 34%).

^{1}H NMR ($CDCl_3$), δ 0.56-0.63 (m, 6H), 1.02 (s, 9H), 2.00-2.10 (m, 4H), 2.18 (s, 3H), 2.31 (s, 3H), 2.51 (d, J = 2.1 Hz, 1H), 2.97-3.06 (m, 1H), 3.65 (dd, J = 3.9, 14.7 Hz, 1H), 3.69-3.75 (m, 1H), 3.86 (t, J = 8.9 Hz, 1H), 4.09 (dd, J = 2.7, 9.4 Hz, 1H), 4.52 (dd, J = 3.8, 11.2 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.86-7.03 (m, 5H), 8.56 (bs, 1H). LC/MS (m/z): calcd. for $C_{29}H_{39}NO_4S$ $(M+H)^+$: 496.6.; found: 496.2.

Example 52 and 53

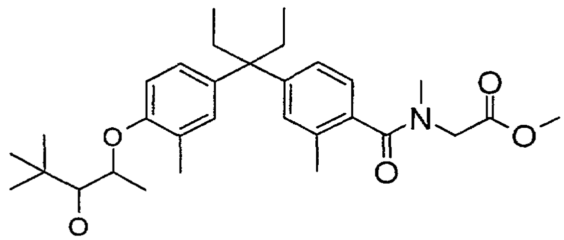
Enantiomer 1 and 2 of [(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.



(Enantiomer 1)

(Enantiomer 2)

A. Racemic [(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester.



Using a procedure analogous to Example 46A, from racemic 4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoic acid (1.46 g, 3.43 mmol) and sascoine methyl ester hydrochloride (0.52 g, 3.76 mmol) to give the title compound (1.74 g, 3.40 mmol, 99%).

^{1}H NMR ($CDCl_3$), δ 0.58-0.65 (m, 6H), 0.97 (s, 6H), 1.02 (s, 3H), 1.33 (d, J = 6.2 Hz, 1H), 1.36 (d, J = 6.2 Hz, 2H), 2.00-2.10 (m, 4H), 2.14 (s, 3H), 2.25 (s, 1H), 2.33 (s, 2H), 2.57 (d, J = 9.6 Hz, 0.33H), 2.58 (d, J = 9.6 Hz, 0.66H), 2.89 (s, 3H), 3.18 (dd, J = 9.6, 1.3 Hz, 1H), 3.69 (s, 1H), 3.79 (s, 2H), 3.91 (s, 0.66H), 4.32 (bs, 1.34H), 4.59 (dq, J = 6.2, 1.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 6.84-7.11 (m, 5H).

ES-MS (m/z): calcd for $C_{31}H_{45}NO_5$ $(M+H)^+$: 512.7; found: 512.3.

B. Separation of enantiomers of [(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester.

A racemic mixture of [(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester (1.73 g), is chromatographed (HPLC: ChiralPak AD, 0.1% TFA in *i*PrOH:Hept = 5 : 95) to give enantiomer 1 (0.636 g, 38%, rt = 21.8 m) and enantiomer 2 (0.72 g, 42%, rt = 26.7 m).

(Enantiomer 1)

HPLC: ChiralPak AD, 0.1% TFA in *i*PrOH:Hept = 5 : 95; 0.6 mL/m (flow rate); rt = 21.8 m; @ 240 nm;

NMR & LC/MS: equivalent to the racemate.

(Enantiomer 2)
HPLC: ChiralPak AD, 0.1% TFA in *i*PrOH:Hept = 5 : 95; 0.60 mL/m (flow rate); rt = 26.7 m; @ 240 nm;
NMR & LC/MS: equivalent to the racemate

C. Enantiomer 1 of [(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.

Using a procedure analogous to Example 46B, enantiomer 1 of [(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester (0.63 g, 1.24 mmol) gives the title compound (0.58 g, 1.16 mmol, 93%).

^{1}H NMR ($CDCl_3$), δ 0.58-0.65 (m, 6H), 0.98 (s, 9H), 1.36 (d, J = 6.2 Hz, 3H), 2.06 (q, J = 7.1 Hz, 4H), 2.14 (s, 3H), 2.25 (s, 0.9H), 2.31 (s, 2.1H), 2.93 (s, 3H), 3.16 (bs, 1H), 3.18 (d, J = 1.3 Hz, 1H), 3.95 (s, 1H), 4.35 (s, 1H), 4.59 (q, J = 6.2 Hz, 1H), 6.68-7.11 (m, 6H).

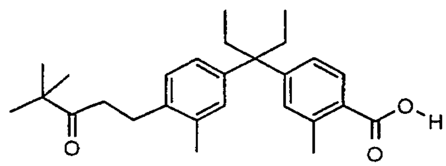
ES-MS (m/z): calcd for $C_{30}H_{42}NO_5$ $(M-H)^-$: 496.7; found: 496.3.

D. Enantiomer 2 of [(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.

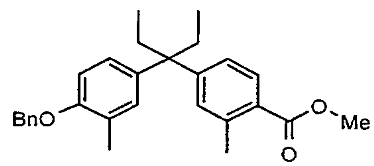
Using a procedure analogous to Example 46B, enantiomer 2 of [(4-{1-ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid methyl ester (0.72 g, 1.41 mmol) gives the title compound (0.64 g, 1.28 mmol, 91%). ^{1}H NMR & ES-MS (m/z): identical to enantiomer 1 of [(4-{1-Ethyl-1-[4-(2-hydroxy-1,3,3-trimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-benzoyl)-methyl-amino]-acetic acid.

Example 54

Preparation of 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.



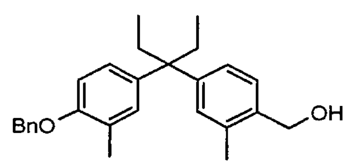
A. 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane.



Using a procedure analogous to Example 1E, 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-trifluoromethanesulfonyloxy-3-methylphenyl]pentane gives the title compound (30 g, 77%).

^{1}H NMR 300 MHz (DMSO-d$_6$): δ 0.54 (t, J = 6.9 Hz, 6H), 2.05 (q , J = 6.9 Hz, 4H), 2.12 (s, 3H), 2.47 (s, 3H), 3.78 (s, 3H), 5.06 (s, 2H), 6.91 (m, 3H), 7.05 (d, J = 8.41 Hz, 1H), 7.11 (s, 1H), 7.29-7.47 (m, 5H), 7.72 (d, J = 8.05, 1H)

B. 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-hydroxymethyl-3-methylphenyl]pentane.

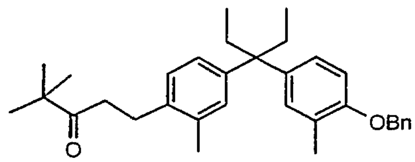


Using a procedure analogous to Example 13B, 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-methoxycarbonyl-3-methylphenyl]pentane gives the title compound (6.0 g, quant).

^{1}H NMR 400 MHz (DMSO-d$_6$): δ 0.54 (t, J = 7.2 Hz, 6H), 2.02 (q , J = 7.2 Hz, 4H), 2.12 (s, 3H), 2.17 (s, 3H), 4.42 (d, J = 6.0 Hz, 2H), 4.94 (t, J = 5.6 Hz, 1H), 5.05 (s, 2H), 6.87-6.94 (m, 5H), 7.19 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 7.6, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.44(d, J = 7.2 Hz, 2H)

High Res. FAB-MS: 388.2397; calc. for $C_{27}H_{32}O_2$: 388.2402.

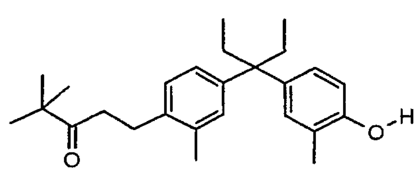
C. 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-benzyloxy-3-methylphenyl]pentane.



To a 0 °C mixture of 3'-[4-benzyloxy-3-methylphenyl]-3'-[4-hydroxymethyl-3-methylphenyl]pentane (6.0 g, 15.4 mmol) and Et_2O (40 ml) is added PBr_3 (1.6 ml, 17.0 mmol). The reaction is stirred for 2 h and allowed to warm to RT. The reaction is diluted with Et_2O, washed with minimal amount of water, brine, Na_2SO_4 dried, concentrated, and azeotrope to dryness with toluene. The resulting residue is dissolved in THF (4 ml) and cooled to -78 °C to afford the bromide/THF solution. In a separate flask is charged with 1M LiHMDS (31 ml, 30.8 mmol), cooled to –78 C, and added pinacolone (3.9 ml, 30.8 mmol). The reaction is stirred for 1.5 h, warmed to –55 C and transferred (via syringe) to the -78 °C solution of bromide/THF. The reaction is allowed to warm to RT and stirred for 16 h. The reaction is diluted with Et2O and washed with 1N HCl. The organic layer is Na2SO4 dried and chromatographed (70% CHCl3/Hex) to give the title compound (5.2 g, 71%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.48 (t, J = 7.6 Hz, 6H), 0.97 (s, 9H), 1.93 (q , J = 7.2 Hz, 4H), 2.05 (s, 3H), 2.13 (s, 3H), 2.60 (t, J = 8.0 Hz, 2H), 2.69 (t, J = 8.4 Hz, 2H), 4.98 (d, J = 4.4 Hz, 2H), 6.77-6.84 (m, 5H), 6.90(d, J = 8.0 Hz, 1H), 7.24-7.26 (m, 1H), 7.32 (t, J = 7.2 Hz, 2H), 7.38 (d, J = 7.2 Hz, 2H).

D. 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane.

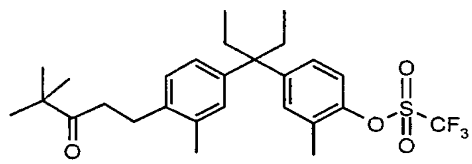


JB5-A03275-010-1

Using a procedure analogous to Example 6D, 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-benzyloxy-3-methylphenyl]pentane gives the title compound (3.1 g, 74%).

^{1}H NMR 400 MHz (DMSO-d$_6$): δ 0.51 (t, J = 6.8 Hz, 6H), 1.03 (s, 9H), 1.96 (q , J = 7.2 Hz, 4H), 2.03 (s, 3H), 2.19 (s, 3H), 2.66 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.73 (dd, J = 2.0 Hz, J = 8.0 Hz, 2H), 6.83-6.86 (m, 2H), 6.95(d, J = 8.0 Hz, 1H), 8.97 (s, J = 8.0 Hz, 1H).

E. 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-(trifluromethylsulfonyloxy)-3-methylphenyl]pentane.

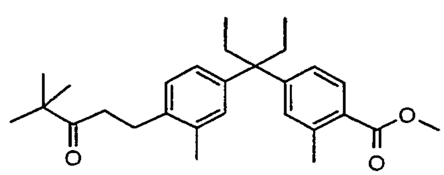


Using a procedure analogous to Example 1C, 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-hydroxy-3-methylphenyl]pentane gives the title compound (4.2 g, quant).

^{1}H NMR 400 MHz (DMSO-d$_6$): δ 0.53 (t, J = 7.2 Hz, 6H), 1.03 (s, 9H), 2.05 (q , J = 7.2 Hz, 4H), 2.21 (s, 3H), 2.27 (s, 3H), 2.66 (t, J = 8.4 Hz, 2H), 2.74 (t, J = 8.0 Hz, 2H), 6.84 (dd, J = 1.6 Hz, J = 6.4 Hz, 1H), 6.91 (s, 1H), 7.00(d, J = 7.6 Hz, 1H), 7.07 (dd, J = 2.0 Hz, J = 6.4 Hz, 1H), 7.21-7.24 (m, 2H).

ES-MS: 530.25 (M+NH4).

F. 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-(methoxycarboxyl)-3-methylphenyl]pentane.



Using a procedure analogous to Example 1E, 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-(trifluoromethylsulfonyloxy)-3-methylphenyl]pentane gives the title compound as a white foam (2.1 g, 67%).

^{1}H NMR 400 MHz (DMSO-d_6): δ 0.53 (t, J = 7.2 Hz, 6H), 1.03 (s, 9H), 2.07 (q , J = 7.2 Hz, 4H), 2.20 (s, 3H), 2.46 (s, 3H), 2.69 (t, J = 7.6 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 3.78 (s, 3H), 6.84 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.98(d, J = 8.0 Hz, 1H), 7.03 (dd, J = 1.6 Hz, J = 6.8 Hz, 1H), 7.08 (s, 1H), 7.70 (d, J = 8.4 Hz, 1H).

High Res ES(+)MS *m/z*: 440.3167; calc. for $C_{28}H_{38}O_3$ + NH_4: 440.3165

G. 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.

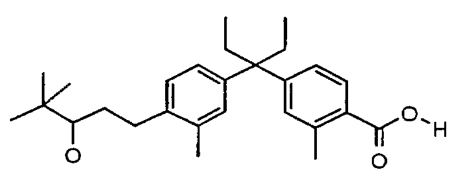
Using a procedure analogous to Example 2, 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-(methoxycarboxyl)-3-methylphenyl]pentane gives the title compound as a white foam (1.5 g, 97%).

^{1}H NMR 300 MHz (DMSO-d_6): δ 0.54 (t, J = 7.0 Hz, 6H), 1.03 (s, 9H), 2.07 (q , J = 6.6 Hz, 4H), 2.20 (s, 3H), 2.46 (s, 3H), 2.68 (d, J = 7.0 Hz, 2H), 2.73 (d, J = 5.9, 2H), 6.85-6.90 (m, 2H), 6.99-7.06 (m, 3H), 7.72 (d, J = 8.4 Hz, 1H).

High Res ES(+)MS *m/z*: 426.3003; calc. for $C_{27}H_{36}O_3$ + NH_4: 426.3008

Example 55

Preparation of racemic 3'-[4-(3-hydroxy-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane.



Using a procedure analogous to Example 1D, 3'-[4-(3-oxo-4,4-dimethylpentyl)-3-methylphenyl]-3'-[4-carboxyl-3-methylphenyl]pentane gives the title compound as a white foam (1.5 g, quant).

^{1}H NMR 300 MHz (DMSO-d_6): δ 0.54 (t, J = 7.3 Hz, 6H), 0.80 (s, 9H), 1.30-1.36 (m, 1H), 1.58-1.64 (m, 1H), 2.07 (q , J = 6.9 Hz, 4H), 2.20 (s, 3H), 2.47 (s, 3H), 2.74-2.82 (m, 1H), 2.99-3.04 (m, 1H), 4.41 (d, J = 6.2, 1H), 6.85-6.89 (m, 2H), 7.02-7.08 (m, 3H), 7.72 (d, J = 8.0 Hz, 1H),

High Res ES(+)MS *m/z*: 428.3145; calc. for $C_{27}H_{38}O_3 + NH_4$: 428.3165

Compounds of the Invention – Salts, Stereoisomers, & Prodrugs:

Salts of the compounds represented by formulae (I) are an additional aspect of the invention. The skilled artisan will also appreciate that the family of compounds of formulae I include acidic and basic members and that the present invention includes pharmaceutically acceptable salts thereof.

In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, ammonium, calcium, magnesium, aluminum, zinc, and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin. For example, a carboxylic acid substituent on the compound of Formula I may be selected as $-CO_2H$ and salts may be formed by reaction with appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium and potassium salt.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, choline, clavulanate, citrate, chloride, chloroprocaine, choline, diethanolamine, dihydrochloride, diphosphate, edetate, edisylate, estolate, esylate, ethylenediamine, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, bromide, chloride, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, malseate, mandelate, meglumine, mesylate, mesviate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pamoate,

pantothenate, phosphate, polygalacturonate, procane, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a chiral column may be used such as those sold by Daicel Chemical Industries identified by the trademarks:
CHIRALPAK AD, CHIRALPAK AS, CHIRALPAK OD, CHIRALPAK OJ, CHIRALPAK OA, CHIRALPAK OB, CHIRALPAK OC, CHIRALPAK OF, CHIRALPAK OG, CHIRALPAK OK, and
CHIRALPAK CA-1.

By another conventional method, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers. These diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

<u>Compounds of the Invention – Salts, Stereoisomers, & Prodrugs:</u>

Salts of the compounds represented by formulae (I) are an additional aspect of the invention. The skilled artisan will also appreciate that the family of compounds of formulae I include acidic and basic members and that the present invention includes pharmaceutically acceptable salts thereof.

In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, ammonium, calcium, magnesium, aluminum, zinc, and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin. For example, a carboxylic acid substituent on the compound of Formula I may be selected as -CO_2H and salts may be formed by reaction with appropriate bases (e.g., NaOH, KOH) to yield the corresponding sodium and potassium salt.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, camsylate, carbonate, chloride, choline, clavulanate, citrate, chloride, chloroprocaine, choline, diethanolamine, dihydrochloride, diphosphate, edetate, edisylate, estolate, esylate, ethylenediamine, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, bromide, chloride, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, malseate, mandelate, meglumine, mesylate, mesviate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pamoate, pantothenate, phosphate, polygalacturonate, procane, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures

as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a chiral column may be used such as those sold by Daicel Chemical Industries identified by the trademarks:
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CHIRALPAK CA-1.

By another conventional method, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers. These diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

The present invention is also embodied in mixtures of compounds of formulae I .

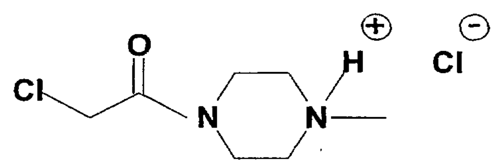
Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters to use as

prodrugs are; methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

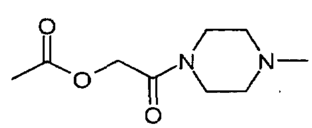
N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No.25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C5,220-3).

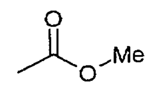
Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula I (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C5,220-3). The prodrugs, for example, may be prepared by reaction of the sodium salt for a compound of Formula I with;



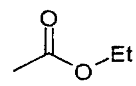
and sodium iodide to provide tthe ester prodrug pendent group



Also, lower alkyl (viz., C_1-C_8) ester prodrugs may be prepared by conventional means such as reacting the sodium or potassium salt (derived by forming the salt of any acidic compound of the invention, viz., reaction of a base such as KOH with an acidic group such as $-CO_2H$) of a compound of Formula I with an alkyl iodide such as methyl iodide, ethyl iodide, n-propyl iodide, isopropyl iodide. Typical ester prodrug substituents are



or



Pharmaceutical Formulations containing the Novel Compounds of the Invention:

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the compound of the invention (compounds of Formula I) together with a pharmaceutically acceptable carrier or diluent. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients.

In making the compositions of the present invention, the compounds of Formula I will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the compound. The compounds of the present invention are preferably formulated prior to administration.

The compounds of the invention may also be delivered by suitable formulations contained in a transderm patch. Alternatively, the compounds of the invention may be delived to a patient by sublingual administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating

agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active ingredient. In tablets the compound of Formula I is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the compound which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The compounds of the invention may be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The compounds can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided compounds of the invention in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Methods of Using the Compounds of the Invention:

Generic disease states benefited by treatment with the compounds of Formula I include, but are not limited to:

disease states characterized by abnormal calcium regulation
disease states characterized by abnormal cell proliferation
disease states characterized by abnormal cell differentiation
disease states characterized by abnormal immune response
disease states characterized by abnormal dermatological conditions
disease states characterized by neurodegenerative condition
disease states characterized by inflammation
disease states characterized by vitamin D sensitivity
disease states characterized by hyperproliferative disorders.

Specific disease states benefited by treatment of the compounds of Formula I and II include, but are not limited to:

Acne
Actinic keratosis
Alopecia
Alzheimer's disease
Bone maintenance in zero gravity
Bone fracture healing
Breast cancer
Chemoprovention of Cancer
Crohn's disease
Colon cancer
Type I diabetes
Host-graft rejection
Hypercalcemia
Type II diabetes
Leukemia
Multiple sclerosis
Myelodysplastic syndrome
Insufficient sebum secretion
Osteomalacia
Osteoporosis
Insufficient dermal firmness
Insufficient dermal hydration
Psoriatic arthritis
Prostate cancer
Psoriasis
Renal osteodystrophy
Rheumatoid arthritis
Scleroderma
Skin cancer

Systemic lupus erythematosus
Skin cell protection from Mustard vesicants
Ulcerative colitis
Vitiligo
Wrinkles

Particularly preferred is the treatment of psoriasis and osteoporosis by administration to a mammal (including a human) of a therapeutically effective amount of compounds of Formulae I. By "pharmaceutically effective amount" it is meant that quantity of pharmaceutical agent corresponding to formulae I which prevents, removes or reduces the deleterious effects of a disease state in mammals, including humans.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a pharmaceutically effective amount typically in the range of from about 0.0001 mg/kg/day to about 50 mg/kg/day of body weight of an active compound of this invention. Preferably the dose of compounds of the invention will be from 0.0001 to 5 mg/kg/day of body weight.

Preferably compounds of the invention (e.g., per Formula I) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.0001 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it is necessary to make routine variations to the dosage depending on the age and condition of the patient. Dosage will also depend on the route of administration. The compounds of the inventiion may be administered by a variety of routes including oral, aerosol, rectal, transdermal, sublingual, subcutaneous, intravenous, intramuscular, and intranasal. Particularly preferred is the treatment of psoriasis with an ointment type formulation containing the compounds of the invention. The ointment formulation may be applied as needed, typically from one to 6 times daily.

Treatment of psoriasis is preferably done with topical application by a formulation in the form of a cream, oil, emulsion, paste or ointment containing a therapeutically effective amount of a compound defined by Formula (I), and in particular those compounds set out in Tables 1 or 2 or those compounds identified as "AA" to "BQ", supra. The formulation for topical treatment contains from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 of a compound defined by formula (I).

For example, two semisolid topical preparations useful as vehicles for VDR modulators in treatment and prevention of psoriasis are as follows:

Polyethylene Glycol Ointment USP (p. 2495)

Prepare Polyethylene Glycol Ointment as follows:

Polyethylene Glycol 3350	400 g.
Polyethylene Glycol 400	600 g.
To make	1000 g.

Heat the two ingredients on a water bath to 65C. Allow to cool, and stir until congealed. If a firmer preparation is desired, replace up to 100 g of the polyethylene glycol 400 with an equal amount of polyethylene glycol 3350.

Hydrophilic Ointment USP (p. 1216)

Prepare Hydrophilic Ointment as follows:

Methylparaben	0.25 g.
Propylparaben	0.15 g.
Sodium Lauryl Sulfate	10 g.
Propylene Glycol	120 g.
Stearyl Alcohol	250 g.
White Petrolatum	250 g.
Purified Water	370 g.
To make about	1000 g.

The Stearyl Alcohol and White Petrolatum are melted on a steam bath, and warmed to about 75C. The other ingredients, previously dissolved in the water are added, warmed to 75C, and the mixture stirred until it congeals.

For each of the above formulations the compound of formula (I) is added during

the heating step in an amount that is from 0.5 to 0.00005 weight percent, preferably from .05 to 0.0005 weight percent, and most preferably from 0.025 to 0.001 weight percent of the total ointment weight. (Source: - United States Pharmacopoeia 24, United States Pharmacopeial Convention, 1999)

Conventional therapy for osteoporosis includes; (i) estrogens, (ii) androgens, (iii) calcium supplements, (iv) vitamin D metabolites, (v) thiazide diuretics, (vi) calcitonin, (vii) bisphosphonates, (viii) SERMS, and (ix) fluorides (see, Harrison's Principles of Internal Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4, pgs.2172-77; the disclosure of which is incorporated herein by reference.). Any one or combination of these conventional therapies may be used in combination with the method of treatment using compounds of Formulae I as taught herein. For example, in a method of treating osteoporosis, the vitamin D receptor modulator compounds of the invention (e.g., as defined by formula I) may be administered separately or simultaneously with a conventional therapy. Alternatively, the vitamin D receptor modulator compounds of the invention may be combined with conventional therapeutic agents in a formulation for treatment of osteoporosis such as set out below:

A formulation for treating osteoporosis comprising:

Ingredient (A1): a vitamin D receptor modulator represented by formula (I), or a pharmaceutically acceptable salt or aliphatic ester prodrug derivative thereof;

Ingredient (B1):

one or more co-agents that are conventional for treatment osteoporosis selected from the group consisting of:

a. estrogens,

b. androgens,

c. calcium supplements,

d. vitamin D metabolites,

e. thiazide diuretics,

f. calcitonin,

g. bisphosphonates,

h. SERMS, and

i. fluorides.

Ingredient (C1): optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A1) to (B1) is from 10:1 to 1:1000 and preferably from 1:1 to 1:100.

Combination Therapy for Psoriasis:

Conventional therapy for psoriasis includes topical glucocorticoids, salicylic acid, crude coal tar, ultraviolet light, and methotrexate (see, Harrison's Principles of Internal Medicine, 13th edition, 1994, published by McGraw Hill Publ., ISBN 0-07-032370-4, pgs. 2172-77). Any one or combination of these conventional therapies may be used in combination with the method of treatment using compounds of Formulae I as taught herein. For example, in a method of treating osteoporosis, the vitamin D receptor modulator compounds of the invention (e.g., as defined by formula I) may be topically administered separately or simultaneously with a conventional therapy. Alternatively, the vitamin D receptor modulator compounds of the invention may be combined with conventional therapeutic agents in a topically applied formulation for treatment of osteoporosis such as set out below:

A formulation for treating osteoporosis comprising:

Ingredient (A2): a vitamin D receptor modulator represented by formula (I), or a pharmaceutically acceptable salt or aliphatic ester prodrug derivative thereof;

Ingredient (B2):

one or more co-agents that are conventional for treatment osteoporosis selected from the group consisting of:

a. topical glucocorticoids ,

b. salicylic acid, or

c. crude coal tar.

Ingredient (C2): optionally, a carrier or diluent.

Typically useful formulations are those wherein the weight ratio of (A2) to (B2) is from 1:10 to 1:100000 and preferably from 1:100 to 1:10000.

Experimental Results:

Table 3

Summary of Experimental Results

Test Cmpd. [1]	RXR-VDR heterodimer[2] EC_{50} (nM)	VDR EC_{50} (nM) (Caco-2 cells)[3]	OCN Promoter [4] EC_{50} (nM)	Mouse Hypercal [5] μg/Kg/d
Ex. 1			21	
Ex. 3A	149/51	1261	15/18	1000
Ex. 3B	396/292	2869	57/83	3000
Ex. 4A			3	
Ex. 4B			15	
Ex. 5		3000	42	100
Ex 6	20/1	300	0.3	10
Ex. 7		63	4	
Ex. 8	1	35	4/1	100
Ex. 9	4	4	7/6	
Ex. 10Da	218/25	538	8/46	
Ex. 10Db	86	935	15	
Ex. 11	186	1011	7	3000
Ex. 12	562/206	1261	20/25	4000
Ex. 12a	67	651	1	300
Ex. 12b	335/55	960	13/23	300
Ex. 13	22/30	1009	89/167	3000
Ex. 14			306	3000

Ex. 15A	229/17	662	35/43	1500
Ex. 15B			163	
Ex. 16			35	>5000
Ex. 17	275/101	990	56/15	>3000
Ex. 18	38/4	430	1/3	1000
Ex. 19	96/12	613	12/16	2000
Ex. 20B	9/3	101	0.8/0.2	300
Ex. 21	226/77	935	8/27	6000
Ex. 22	80/23	467	7/3	1000
Ex. 23	283/230	805	13/40	3000
Ex. 24	3	368	0.2	
Ex. 25A	8/2	340	0.4	<300
Ex. 25B	83/25	982	2/3	1000
Ex. 26	6/67	651	1	300
Ex. 27	335/55	960	13/23	300
Ex. 28	171/337	72	106/84	
Ex. 29	93/60	958	2/11	3000
Ex. 30	101/48	698	1/3	1000
Ex. 31	19/33	410	1	3000
Ex. 32	89/9	345	4/1	1000
Ex. 33	1/55	418	3/1	<300
Ex. 34	15/5	303	9/1	<300
Ex. 35			27	

Ex. 36	242/293	698	135/37	>300
Ex. 37	60	698	12	1000
Ex. 38	266/137	863	41	
Ex. 39	302/204	979	74/61	
Ex. 40	138	694	70	
Ex. 41	523		421	
Ex. 42	56/316	1227	98/19	
Ex. 44	0.4		0.1	<300
Ex. 45	2		0.7	300
Ex. 46	6	400	2/3	3000
Ex. 47	59	816	22/6	3000
Ex. 48	44	433	9/4	<1000
Ex. 49	92	859	14/40	
Ex. 50	10	83	0.2	300
Ex. 51	4		1.4	300
Ex. 52	81	813	4	>3000
Ex. 53	236/210		12/34	>3000
Ex. 54	396		119	>3000
Ex. 55	9	920	6	
AA	5.02	16	5	0.06
BB	10.32	169.81	8.24	20
CC	2427.7		>1000	
DD	109.44		31.1	1000
EE	429.99	891.16	341.25	1000
FF	3	57		

Table 4

Summary of Experimental Results

Test Cmpd. [1]	Kera. Prolif. IC_{50} (nM)	IL-10. IC_{50} (nM)
Ex. 1		
Ex. 3A		
Ex. 3B		
Ex. 4A		
Ex. 4B		
Ex. 5	375	
Ex 6	2	55
Ex. 7	18	
Ex. 8	330	
Ex. 9	985	
Ex. 10Da	1000	
Ex. 10Db	1000	
Ex. 11	308	478
Ex. 12		
Ex. 12a	4	52
Ex. 12b		
Ex. 13		
Ex. 14		
Ex. 15A	117	

Ex. 15B		
Ex. 16		
Ex. 17	1000	
Ex. 18	1000	47
Ex. 19	82	142
Ex. 20B	3	4
Ex. 21	223	1050
Ex. 22	4	39
Ex. 23	40	27
Ex. 24		
Ex. 25A	1105	40
Ex. 25B	26	158
Ex. 26	4	52
Ex. 27		
Ex. 28	240	
Ex. 29	49	153
Ex. 30	20	123
Ex. 31	21	295
Ex. 32	1000	106
Ex. 33	6	19
Ex. 34	25	45
Ex. 35	40	
Ex. 36	139	

Ex. 37	55	229
Ex. 38		
Ex. 39	508	
Ex. 40	1000	
Ex. 41		
Ex. 42	50	
Ex. 44	28	6
Ex. 45	32	15
Ex. 46	21	33
Ex. 47	1000	
Ex. 48	1000	
Ex. 49	1000	
Ex. 50	3	4
Ex. 51	26	19
Ex. 52	52	154
Ex. 53	224	
Ex. 54		
Ex. 55		
AA	120	1.2
BB	10	28
CC		
DD	1060	
EE		
FF	103	0.5

Explanation of Table 5 and 6 column numerical superscripts:

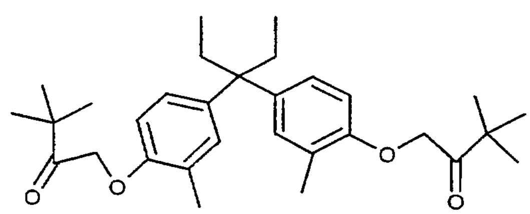
1. Test Compound numbers refer to the products of the corresponding Example Nos. that is, compounds within the scope of the invention. For example, the number "Ex. 2" refers to the compound, 3'-[4-(2-hydroxy-3,3-dimethylbutoxy) -3-methylphenyl]-3'-[5-methoxycarbonyl-4-methylthiophen-2-yl]pentane, prepared in Example 2. The control experiments are done with the double letter coded compounds identified as follows:

"AA" = 1α,25-dihydroxyvitamin D_3

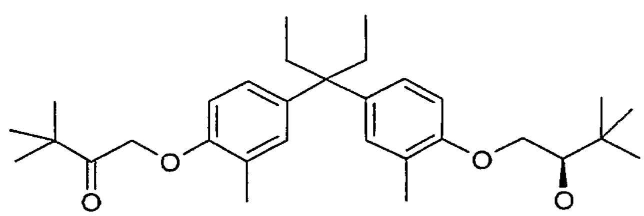
"BB" = 3-(4-{1-Ethyl-1-[4-(2-hydroxy-3,3-dimethyl-butoxy)-3-methyl-phenyl]-propyl}-2-methyl-phenoxy)-propane-1,2-diol

"CC" = 1-(4-{1-[4-(3,3-Dimethyl-2-oxo-butoxy)-3-methyl-phenyl]-cyclohexyl}-2-methyl-phenoxy)-3,3-dimethyl-butan-2-one

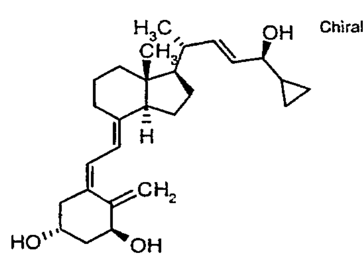
"DD" = compound represented by the formula:



"EE" = compound represented by the formula:



"FF" -= calcipotriol (structural formula below):



2. The RXR-VDR heterodimerization (SaOS-2 cells) test is described in the "Assay" section of the Description, infra.

3. The VDR CTF (Caco-2 cells) test is described in the "Assay" section of the Description, infra.

4. The OCN Promoter test is described in the "Assay" section of the Description, infra.

5. The Mouse Hypercalcemia test is described in the "Assay" section of the Description, infra.

6. The keratinocyte proliferation assay is described in the "Assay" section of the Description, infra.

7. The IL-10 induction assay is described in the "Assay" section of the Description, infra.

Assay Methods

Use of the Assay Methods:

The evaluation of the novel compounds of the invention for osteoporosis and other related diseases is done using a plurality of test results. The use of multiple assays is necessary since the combined properties of (i) high activity for the vitamin D receptor, and (ii) prevention of hypercalcemia must be achieved to have utility for the methods of treating diseases, which are also, aspects of this invention. Some of the tests described below are believed related to other tests and measure related properties of compounds. Consequently, a compound may be considered to have utility in the practice of the invention if is meets most, if not all, of the acceptance criteria for the above described tests.

The evaluation of the novel compounds of the invention for psoriasis is done using the Keratinocyte Proliferation Assay in combination with other assays that measure inhibition of IL-2 production and stimulation of IL-10 production in peripheral blood mononuclear cells (PBMCs).

Brief Description, Utility and Acceptance Criteria for the Assay Methods:

1. The RXR-VDR heterodimerAssay:

This assay provides the VDR activity of a test compound. It is desirable to have low EC50 values for a compound in this assay. The lower the EC50 value, the more active the compound will be as a VDR agonist. Desired assay results

are EC50 values less than or equal to 600 nM. Preferred assay results are less than 250 nM, and most preferably less than 150 nM.

2. The Caco-2 cell Co-transfection Assay:

The Caco-2 cell assay is an indicator for the undesirable condition of hypercalcemia. This co-transfection assay is a surrogate assay for in vivo calcemic activity of VDR ligands. It is desirable to have high EC50 values for a test compound in this assay. The higher the EC50 values for a compound the less calcemic it will be in vivo. Desired assay results are EC50 greater than or equal to 300 nM. Preferred assay results are greater than 1000 nM.

3. The OCN (osteocalcin) Promoter Assay

The OCN Promoter Assay is an indicator and marker for osteoporosis. Desired assay results are EC50 less than or equal to 325 nM. Preferred assay results are less than 50 nM.

4. The Mouse Hypercalcemia Assay

The Mouse Hypercalcemia Assay is a six day hypercalcemia test for toxicity and selectivity. Acceptable test results are levels greater than 300 μg/kg/day. Preferred assay results are levels greater than 1000 μg/kg/day.

5. The Keratinocyte Proliferation Assay

This Assay is indicative for the treatment of psoriasis. An acceptable test result is IC50 value of less than or equal to 300 nM. Preferred assay results are IC50 values of less than 100 nM.

6. The IL-10 induction Assay

This is an in vitro efficacy assay for psoriasis, abscess and adhesion. Psoriasis involves both keratinocytes and immune cells. IL-10 is a unique cytokine because it is anti-inflammatory and immunosuppressive. This assay tells us whether a VDRM is able to function as an agonist in PBMCs (primary blood mononuclear cells) or not. A lower EC50 value is desirable in this assay since a compound with a lower EC50 value will be a

better agonist in PBMCs. An acceptable test result is an EC50 value of less than 200 nM. Preferred assay results are EC50 values of less than 100 nM.

7. Other Compound Assay Standards

An alternative measure of the therapeutic index (bone efficacy vx. Hypervcalcemia) of compounds of the invention for treatment of osteoporosis is a numerical ratio calculated as follows:

Dose Threshold needed to induce hypercalcemia

divided by

Dose Threshold needed for bone efficacy

An alternative measusre of the therapeutic index (in vivo keratinocyte proliferation vs. hypercalcemia) of compounds of the invention for treatment of psoriasis is a numerical ratio calculated as follows:

Dose Threshold needed to induce hypercalcemia

divided by

Dose Threshold needed to induce keratinocyte proliferation

For the above ratios, Dose Thresholds are determined from dose response curve data.

Details of the Assay Methods:

(1) Materials and Method for RXR-VDR Heterodimerization Assay:

Transfection Method:

• FuGENE 6 Transfection Reagent (Roche Cat # 1 814 443)

Growth Media:

• D-MEM High Glucose (Gibco BRL Cat # 11054-020), 10% FBS, 1% antibiotic-antimycotic (Ab-Am)

FBS heat inactivated (Gibco BRL Cat # 10092-147)

Ab-Am (Gibco BRL Cat # 15240-062)

Cells:

• Grow SaOs-2 cells in T-152 cm^2 culture flasks in *growth media.*

• Keep the density at 5-6 x 10^5 cells/ml

• Passage cells 1:3 twice a week

• Add Trypsin EDTA (Gibco BRL Cat # 25300-020)and incubate

• Resuspend cells in plating media and transfer into growth media.

Wash Media:

• HBSS Low Glucose Without Phenol Red (Gibco BRL Cat # 14175-095), 1% Ab-Am

Plating Media:

• D-MEM Low Glucose Without Phenol Red (Gibco BRL Cat # 11054-020), 1% Ab-Am

D-MEM

Stripped FBS (Hyclone Cat# SH30068.03 Lot # AHM9371)

Ab-Am

Transfection / Treatment Media:

• D-MEM Low Glucose Without Phenol Red only

T-152 cm^2 culture flask:

• Use Corning Coastar T-152 cm^2 culture flask (Cat # 430825) to grow the cells

Flat well Plates:

• Use well plate to plate cells

• Use Deep well plate sterile to make up treatment media.

Luciferase Assay Reagent:

• Use Steady-Glo Luciferase Reagent from Promega (Cat # E2550) Consists of:

a. E2533 Assay Substrate, lyopholized product and

b. E2543 Assay Buffer.

• Thaw at room temperature

• Store

DAY 1: Cell Plating:

Cell Harvesting

Aspirate media from culture flask, rinse cells with HBSS and aspirate.

Add trypsin and incubate.

When cells appear detached, resuspend cells in *growth media.*

Transfer into a new flask with fresh *growth media* for passaging the cells.

Plate well plates and two extra plates

D. Cell Count

Mix the cell suspension using pipette

Use *Hematocytometer* to count the cells

Load cell suspension onto the hemocytometer chamber

Count cells.

Plate seeding:

Use plating media 10 % Stripped FBS in D-MEM Low Glucose, Without Phenol Red, 1% Ab-Am

Plate 14 plates @ 165 µl / well.

In sterile flask add cell suspension to *plating media.*

Mix.

Add cells / well.

Place the cells in the incubator.

Cells should be about 75 % confluent prior to transfection.

Step 1: DNA and Media

Add plain DMEM media to tubes for mixing the DNA

Add the Reporter gene pFR-LUC

Add the Gal4-RXR-DEF and VP16-VDR-LBD

Step 2: FuGENE and Media

Prepare plain DMEM media in a ubes for mixing FuGENE

Add *FuGENE 6 Transfection Reagent*

Incubate

Step 3: FuGENE , DNA and Media Complex

Add FuGENE Media complex from step 2 to DNA Media complex from step1

Incubate

Step 4: FuGENE , DNA and Media Complex to-well plate

Add FuGENE-DNA-Media complex from step 3 to each plate

Incubate.

Day 3: Dosing

Treatment preparation

Allow for transfection time

Make a stock solution of the compounds in DMSO

Vortex until all the compounds has been dissolved.

Further dilute in D-MEM (Low Glucose – With out Phenol Red)

Add compounds in quadruplicate to give final volume

Incubate.

Day 4: Luciferase Assay

Read the plates after drug treatment

Remove part of media from all the wells and leave remainder

Add Steady-Glo Luciferase Reagent mixture / wells

Incubate

Count each well using a Luminescence counter, Top Count NXT by Packard

Set a delay between plates to reduce the background.

(2) Materials and Method for The Caco-2 Cell Assay:

Caco-2 cells, grown in phenol red free, DMEM (Invitrogen, Carlsbad, CA) containing 10 % charcoal-stripped FCS (Hyclone, Logan, UT), were transfected with Fugene 6 reagent (Roche Diagnostics, Indianapolis, IN). Cells (5000/well) were plated 18 h before transfection in a 96 well plate. The Cells were transfected with Gal4-responsive reporter pFRLuc (150 ng, Stratagene, La Jolla CA) and the receptor expression vector pGal4-VDR-LBD (10 ng), along with Fugene 6 reagent (0.2 µl/well). The DNA-Fugene complex was formed by incubating the mixture for 30 min at room temperature. The cells were transfected in triplicate for 5 h, and treated with various concentrations of VDR ligands (form 0.01 nM to 10,000 nM concentration range) 18h post-transfection. The luciferase activity was quantified using Steady-Glo reagent kit (Promega, Madison, WI) as per manufacturer's specifications.

(3) Materials and Method for The OCN Promoter Assay:

The activation of osteocalcin by VDR ligands was evaluated in a rat osteoblast-like cell line RG-15 (ROS 17/2.8) stably expressing rat osteocalcin promoter fused with luciferase reporter gene. The stable cell lines were established as reported before (Activation of Osteocalcin Transcription involves interaction of protein kinase A- and Protein kinase C-dependent pathways. Boguslawski, G., Hale, L. V., Yu, X.-P., Miles, R. R., Onyia, J. E., Santerre R. F., Chandrasekhar, S. J Biol. Chem. 275, 999-1006, 2000). Confluent RG-15 cells maintained in DMEM/F-12 medium (3:1) containing 5% FBS, 300 □g/ml G418 and at 37°C under 5% CO_2/95% air atmosphere were trypsinized (0.25% trypsin) and plated into white opaque 96-well cell culture plates (25000 cells/well). After 24 hr, cells (in DMEM/F-12 medium + 2% FBS) were treated with various concentrations of compounds, dissolved in DMSO. The final DMSO concentration remained at 0.01% (v/v). After 48 hr treatment, the medium was removed, cells were lysed with 50 □l of lysis buffer (From Luciferase reporter assay system, Roche Diagnostics, Indianapolis, IN) and assayed for luciferase activity using the Luciferase Reporter Gene Assay kit from Boehringer Mannheim as per manufacturer's specifications.

(4) Materials and Method for The Mouse Hypercalcemia Assay:

Weanling, virus -antibody-free, five to six weeks old female DBF mice (Harlan, Indianapolis, IN) are used for all the studies. Animals are allowed to acclimate to local vivarium conditions for 2 days. Mice are maintained on a 12 hr light/dark cycle at 22°C with ad lib access to food (TD 5001 with 1.2% Ca and 0.9%P, Teklad, Madison, WI) and water. The animals then are divided into groups with 4-5 mice per group. Different doses of test compounds prepared in 10% Ethanol and 90% sesame oil are administered to mice orally via gavage for 6 days. 1α-25$(OH)_2D_3$ 0.5μg/kg/d was also given to one group of mice as the positive control. Serum ionized calcium is evaluated at 6 hours after the last dosing under isoflurane anesthesia by Ciba-Corning Ca++/PH Analyzer, (Model 634, Chiron Diagnostics Corp., East Walpole, MA). Raw data of group differences is assessed by analysis of variance (ANOVA) using Fisher's protected least significant difference (PLSD) where the significance level was $P < 0.05$.

(5) <u>The Keratinocyte Proliferation Assay:</u>

KERtr cells (Human skin keratinocyte transformed with a retrovirus vector, obtained from ATCC) were plated in 96-well flat-bottomed plates (3000 cells/well) in 100 □l keratinocyte serum free medium supplemented with bovine pituitary extract in the absence of EGF (Life Technologies, Rockville, MD) and incubated at 37°C for two days. The cells were treated with various concentrations of VDR ligands (ten-fold serial dilution from 10,000 nM to 0.1 nM in triplicate), dissolved in 100 □l keratinocyte serum free medium supplemented with bovine pituitary extract in the absence of EGF and incubated at 37°C for 72hr. BrdU (5-bromo-2'-deoxyuridine) incorporation was analyzed as a measure of DNA replication (Cell proliferation ELISA kit, Roche Diagnostics, Indianapolis, IN) and absorbance was measured at 405 nm. Potency values (IC_{50}) values were determined as the concentration (nM) of compound that elicited a half-maximal response.

<u>(6) Materials and Method for human IL-10 Induction Assay:</u>

Isolation of peripheral blood mononuclear cells (PBMCs):

A. Collect 50 ml of human blood and dilute with media, RPMI-1640.

B. Prepare sterile tubes with ficol.

C. Add diluted blood to tubes.

D. Centrifuge.

E. Discard the top layer and collect the cells from middle layer.

F. Divide all cells into four tubes and add media.

G. Centrifuge.

H. Aspirate off media and resuspend.

I. Collect all cells

J. Centrifuge. at 1200 rpm for 10 minutes.

K. Resuspend in RPMI-1640 with 2% FBS and count cells

Stimulation of PBMC:

L. Prepare TPA in DMSO.

M. Dissolve PHA in water .

N. Plate TPA/PHA treated PBMCs in well plates.

O. Incubate.

Treatment:

P. Prepare all compound dilutions in plain RPMI- 1640 media.

Q. Add diluted compound.

R. Incubate.

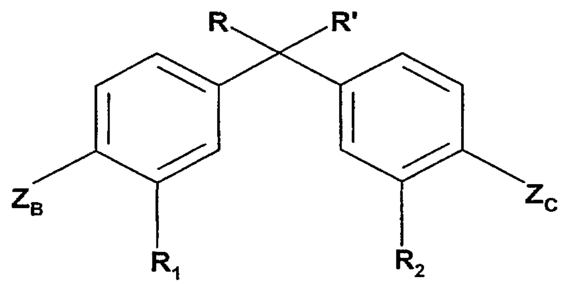
Sample Collection and assay:

S. Remove all the cells by centrifugation and assay the supernatant for IL-10 by immunoassay.

1) T. Perform IL-10 assay using anti-human IL-10 antibody coated beads, as described by the manufacturer (Linco Research Inc., St. Charles, MO).

WE CLAIM:

1. A compound represented by formula I or a pharmaceutically acceptable salt or a prodrug derivative thereof:



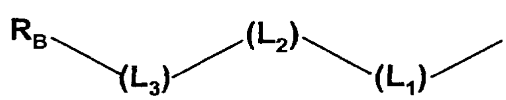
(I)

wherein;

R and R' are independently C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, or together R and R' form a substituted or unsubstituted, saturated or unsaturated carbocyclic ring having from 3 to 8 carbon atoms;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halo, C_1-C_5 alkyl, C_1-C_5 fluoroalkyl, -O-C_1-C_5 alkyl, -S-C_1-C_5 alkyl, -O-C_1-C_5 fluoroalkyl, -CN, -NO_2, acetyl, -S-C_1-C_5 fluoroalkyl, C_2-C_5 alkenyl, C_3-C_5 cycloalkyl, and C_3-C_5 cycloalkenyl;

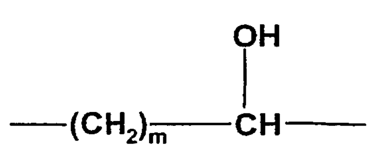
Z_B is a group represented by the formula:



wherein

-(L_1), -(L_2)-, and -(L_3)- is each a divalent linking groups independently selected from the group consisting of

a bond ,



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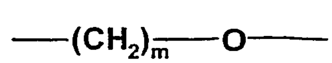

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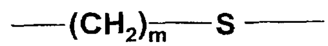
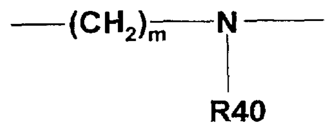
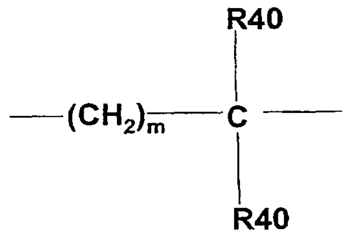
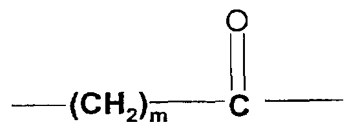
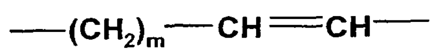
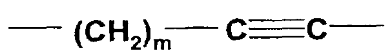
 ,

 ,

 ,

 ,

 , and

 ,

where m is 0, 1, or 2, and each R40 is independently hydrogen, C_1-C_5 alkyl, or C_1-C_5 fluoroalkyl;

R_B is a branched C_3-C_5 alkyl;

Z_C is carbon atom linked group selected from:

$-CO_2H$,

$-CO_2Me$,

$-CO_2Et$,

$-C(O)CH_2S(O)Me$,

$-C(O)CH_2S(O)Et$,

$-C(O)CH_2S(O)_2Me$,

$-C(O)CH_2S(O)_2Et$,

$-C(O)CH_2CH_2S(O)Me$,

$-C(O)CH_2CH_2S(O)Et$,

$-C(O)CH_2CH_2S(O)_2Me$,

$-C(O)CH_2CH_2S(O)_2Et$,

$-C(O)CH(Me)CH_2CO_2H$,

-C(O)CH(Me)CH$_2$CO$_2$Me,
-C(O)CH(Me)CH$_2$CO$_2$Et,
-C(O)CH(Me)CH$_2$CO$_2$iPr,
-C(O)CH(Me)CH$_2$CO$_2$tBu,
-C(O)CH(Me)CH(Me)CO$_2$H,
-C(O)CH(Me)CH(Me)CO$_2$Me,
-C(O)CH(Me)CH(Me)CO$_2$Et,
-C(O)CH(Me)CH(Me)CO$_2$iPr,
-C(O)CH(Me)CH(Me)CO$_2$tBu,
-C(O)CH(Me)C(Me)$_2$CO$_2$H,
-C(O)CH(Me)C(Me)$_2$CO$_2$Me,
-C(O)CH(Me)C(Me)$_2$CO$_2$Et,
-C(O)CH(Me)C(Me)$_2$CO$_2$iPr,
-C(O)CH(Me)C(Me)$_2$CO$_2$tBu,
-C(O)CH(Me)CH(Et)CO$_2$H,
-C(O)CH(Me)CH(Et)CO$_2$Me,
-C(O)CH(Me)CH(Et)CO$_2$Et,
-C(O)CH(Me)CH(Et)CO$_2$iPr,
-C(O)CH(Me)CH(Et)CO$_2$tBu,
-C(O)C(O)OH,
-C(O)C(O)NH$_2$,
-C(O)C(O)NHMe,
-C(O)C(O)NMe$_2$,

-C(O)NH_2,
-C(O)NMe_2,
-C(O)NH-CH_2-C(O)OH,
-C(O)NH-CH_2-C(O)OMe,
-C(O)NH-CH_2-C(O)OEt,
-C(O)NH-CH_2-C(O)OiPr,
-C(O)NH-CH_2-C(O)OtBu,
-C(O)NH-CH(Me)-C(O)OH,
-C(O)NH-CH(Me)-C(O)OMe,
-C(O)NH-CH(Me)-C(O)OEt,
-C(O)NH-CH(Me)-C(O)iPr,
-C(O)NH-CH(Me)-C(O)tBu,
-C(O)NH-CH(Et)-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OMe,
-C(O)NH-C$(Me)_2$-C(O)OEt,
-C(O)NH-C$(Me)_2$-C(O)iPr,
-C(O)NH-C$(Me)_2$-C(O)tBu,
-C(O)NH-CMe(Et)-C(O)OH,
-C(O)NH-CH(F)-C(O)OH,
-C(O)NH-CH(CF_3)-C(O)OH,
-C(O)NH-CH(OH)-C(O)OH,
-C(O)NH-CH(cyclopropyl)-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OH,
-C(O)NH-C$(Me)_2$-C(O)OH,
-C(O)NH-CF(Me)-C(O)OH,
-C(O)NH-C(Me)(CF_3)-C(O)OH,
-C(O)NH-C(Me)(OH)-C(O)OH,
-C(O)NH-C(Me)(cyclopropyl)CO_2H
-C(O)NMe-CH_2-C(O)OH,
-C(O)NMe-CH_2-C(O)OMe,
-C(O)NMe-CH_2-C(O)OEt,

-C(O)NMe-CH_2-C(O)OiPr,
-C(O)NMe-CH_2-C(O)tBu,
-C(O)NMe-CH_2-C(O)OH,
-C(O)NMe-CH(Me)-C(O)OH,
-C(O)NMe-CH(F)-C(O)OH,
-C(O)NMe-CH(CF_3)-C(O)OH,
-C(O)NMe-CH(OH)-C(O)OH,
-C(O)NMe-CH(cyclopropyl)-C(O)OH,
-C(O)NMe-C$(Me)_2$-C(O)OH,
-C(O)NMe-CF(Me)-C(O)OH,
-C(O)NMe-C(Me)(CF_3)-C(O)OH,
-C(O)NMe-C(Me)(OH)-C(O)OH,
-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH,
-C(O)NHS(O)Me,
-C(O)NHSO_2Me,
-C(O)-NH-5-tetrazolyl,
-C(O)NHS(O)Me,
-C(O)NHS(O)Et,
-C(O)NHSO_2Me,
-C(O)NHSO_2Et,
-C(O)NHS(O)iPr,
-C(O)NHSO_2iPr,
-C(O)NHS(O)tBu,
-C(O)NHSO_2tBu,
-C(O)NHCH_2S(O)Me,
-C(O)NHCH_2S(O)Et,
-C(O)NHCH_2SO_2Me,
-C(O)NHCH_2SO_2Et,
-C(O)NHCH_2CH_2S(O)Me,
-C(O)NHCH_2CH_2S(O)Et,
-C(O)NH$CH_2CH_2SO_2$Me,
-C(O)NH$CH_2CH_2SO_2$Et,

-C(O)N(Me)S(O)Me,

-C(O)N(Me)SO_2Me,

-C(O)-N(Me)-5-tetrazolyl,

-C(O)N(Me)S(O)Me,

-C(O)N(Me)S(O)Et,

-C(O)N(Me)SO_2Me,

-C(O)N(Me)SO_2Et,

-C(O)N(Me)S(O)iPr,

-C(O)N(Me))SO_2iPr,

-C(O)N(Me))S(O)tBu,

-C(O)N(Me)SO_2tBu,

-C(O)N(Me)CH_2S(O)Me,

-C(O)N(Me)CH_2S(O)Et,

-C(O)N(Me)CH_2SO_2Me,

-C(O)N(Me)CH_2SO_2Et,

-C(O)N(Me)CH_2CH_2S(O)Me,

-C(O)N(Me)CH_2CH_2S(O)Et,

-C(O)N(Me)$CH_2CH_2SO_2$Me,

-C(O)N(Me)$CH_2CH_2SO_2$Et,

-CH_2CO_2H,

-CH_2-5-tetrazolyl,

-CH_2CO_2Me,

-CH_2CO_2Et,

-CH_2NHS(O)Me,

-CH_2NHS(O)Et,

-CH_2NHSO_2Me,

-CH_2NHSO_2Et,

-CH_2NHS(O)iPr,

-CH_2NHSO_2iPr,

-CH_2NHS(O)tBu,

-CH_2NHSO_2tBu,

-$CH_2NHCH_2CH_2SO_2CH_3$,

$-CH_2NH(CH_2CO_2H)$,
$-CH_2N(C(O)Me)(CH_2CO_2H)$,
$-CH_2$-N-pyrrolidin-2-one,
$-CH_2$-(1-methylpyrrolidin-2-one-3-yl),
$-CH_2S(O)Me$,
$-CH_2S(O)Et$,
$-CH_2S(O)_2Me$,
$-CH_2S(O)_2Et$,
$-CH_2S(O)iPr$,
$-CH_2S(O)_2iPr$,
$-CH_2S(O)tBu$,
$-CH_2S(O)_2tBu$,
$-CH_2CO_2H$, $CH_2C(O)NH_2$,
$-CH_2C(O)NMe_2$,
$-CH_2C(O)NHMe$,
$-CH_2C(O)$-N-pyrrolidine,
$-CH_2S(O)_2Me$, $CH_2S(O)Me$,
$-CH(OH) CO_2H$,
$-CH(OH)C(O)NH_2$,
$-CH(OH)C(O)NHMe$,
$-CH(OH)C(O)NMe_2$,
$-CH(OH)C(O)NEt_2$,
$-CH_2CH_2CO_2H$,
$-CH_2CH_2CO_2Me$,
$-CH_2CH_2CO_2Et$,
$-CH_2CH_2C(O)NH_2$,
$-CH_2CH_2C(O)NHMe$,
$-CH_2CH_2C(O)NMe_2$,
$-CH_2CH_2$-5-tetrazolyl,
$-CH_2CH_2S(O)_2Me$,
$-CH_2CH_2S(O)Me$,
$-CH_2CH_2S(O)_2Et$,

$-CH_2CH_2S(O)Et$,

$-CH_2CH_2S(O)iPr$,

$-CH_2CH_2S(O)_2iPr$,

$-CH_2CH_2S(O)tBu$,

$-CH_2CH_2S(O)_2tBu$,

$-CH_2CH_2S(O)NH_2$,

$-CH_2CH_2S(O)NHMe$,

$-CH_2CH_2S(O)NMe_2$,

$-CH_2CH_2S(O)_2NH_2$,

$-CH_2CH_2S(O)_2NHMe$

$-CH_2CH_2S(O)_2NMe_2$,

$-CH_2CH_2CH_2S(O)Me$,

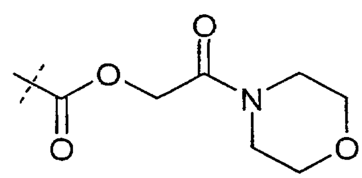
$-CH_2CH_2CH_2S(O)Et$,

$-CH_2CH_2CH_2S(O)_2Me$,

$-CH_2CH_2CH_2S(O)_2Et$,

-C(O)OH,

-5-tetrazolyl,



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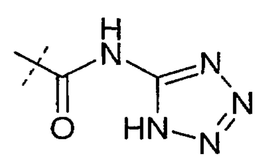

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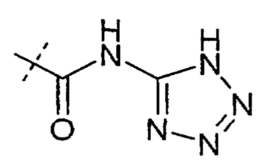

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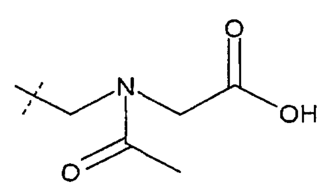

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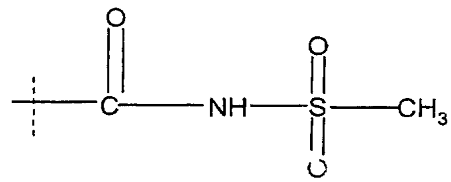

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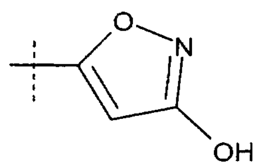

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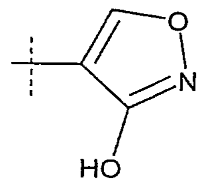

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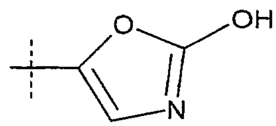

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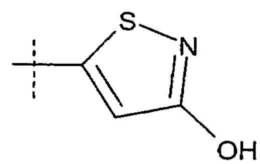

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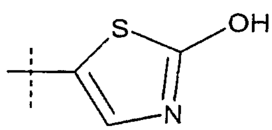

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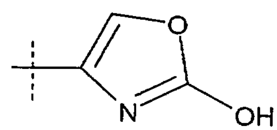

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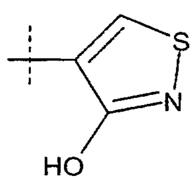

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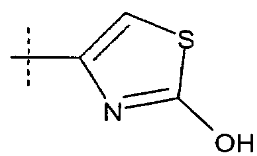

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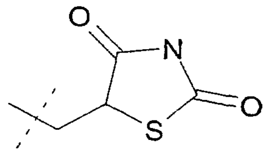
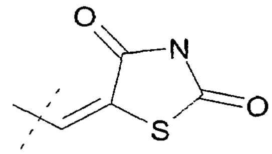
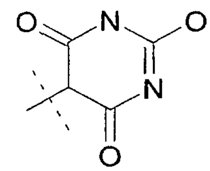
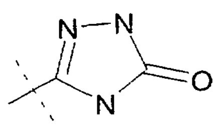
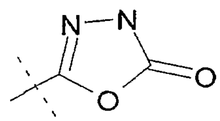
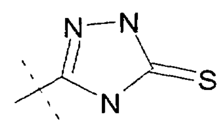
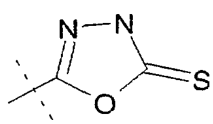
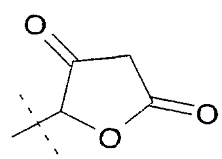
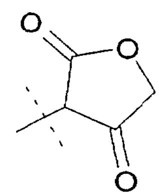
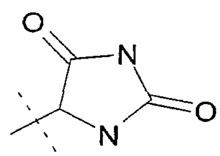
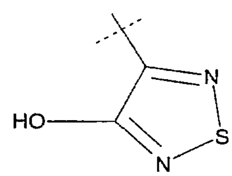
 ,  ,  ,

 ,  ,  ,

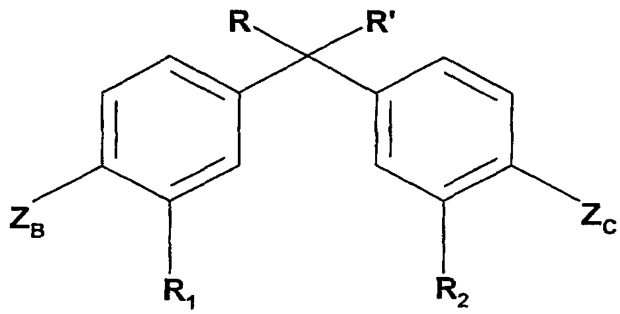
 ,  ,  ,

 ,



-1,3,4-oxadiazolin-2-one-5-yl,
-imidazolidine-2,4-dione-5-yl,
-isoxazol-3-ol-yl, or
-1,3,4-oxadiazolin-2-thione-5-yl.

2. A compound represented by formula I or a pharmaceutically acceptable salt or a prodrug derivative thereof:



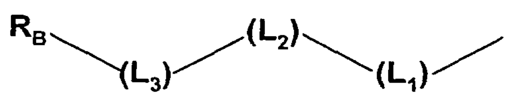
(I)

wherein;

R and R' are independently methyl, ethyl, propyl, or 1-methylethyl;

R_1 and R_2 are independently selected from the group consisting of hydrogen, fluoro, -Cl, $-CF_3$, $-CH_2F$, $-CHF_2$, methoxy, ethoxy, vinyl, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl, 1-methylpropyl, 2-methylpropyl, or cyclopropyl;

Z_B is a branched alkyl terminated group represented by the formula:



R_B is 1-methylethyl; 1-methylpropyl; 2-methylpropyl; 1,1-dimethylethyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; 2,2-dimethylpropyl; 3-methyl-3-hydroxy-4,4-dimethylpentyl; 3-methyl-3-hydroxy-4,4-dimethylpentenyl; 3-methyl-3-hydroxy-4,4-dimethylpentyl; 3-ethyl-3-hydroxy-4,4-dimethylpentynyl; 3-ethyl-3-hydroxy-4,4-dimethylpentenyl; or 3-ethyl-3-hydroxy-4,4-dimethylpentynyl;

(L_1) and (L_2) and (L_3) are independently divalent linking groups where

L_1 is –O-, $-CH_2$-, C(O)- , -CHOH-, –CH(Me)- , or -C(Me)OH- ;

L_2 is $-CH_2$- , -C(O)- , -CHOH-, –CH(Me)- , or -C(Me)OH- ; or

L_1 and L_2 taken together is the group

$$-CH_2-CH_2- \quad ,$$

$$-CH{=}CH- \quad , \text{or}$$

$$-C{\equiv}C- \quad ;$$

L_3 is a bond, $-CH_2-$, -CHOH- , –CH(Me)-, -C(O)-, or -C(Me)OH- ;

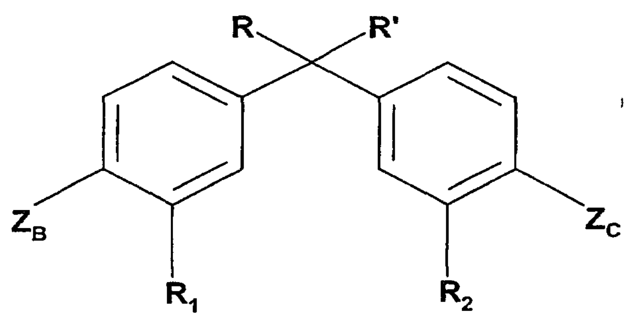
Z_C is a group selected from

$-C(O)CH_2S(O)Me$,
$-C(O)CH_2S(O)Et$,
$-C(O)CH_2S(O)_2Me$,
$-C(O)CH_2S(O)_2Et$,
$-C(O)CH_2CH_2S(O)Me$,
$-C(O)CH_2CH_2S(O)Et$,
$-C(O)CH_2CH_2S(O)_2Me$,
$-C(O)CH_2CH_2S(O)_2Et$,
$-C(O)CH(Me)CH_2CO_2H$,
$-C(O)CH(Me)CH_2CO_2Me$,
$-C(O)CH(Me)CH_2CO_2Et$,
$-C(O)CH(Me)CH_2CO_2iPr$,
$-C(O)CH(Me)CH_2CO_2tBu$,
$-C(O)CH(Me)CH(Me)CO_2H$,
$-C(O)CH(Me)CH(Me)CO_2Me$,
$-C(O)CH(Me)CH(Me)CO_2Et$,
$-C(O)CH(Me)CH(Me)CO_2iPr$,
$-C(O)CH(Me)CH(Me)CO_2tBu$,
$-C(O)CH(Me)C(Me)_2CO_2H$,
$-C(O)CH(Me)C(Me)_2CO_2Me$,
$-C(O)CH(Me)C(Me)_2CO_2Et$,
$-C(O)CH(Me)C(Me)_2CO_2iPr$,
$-C(O)CH(Me)C(Me)_2CO_2tBu$,
$-C(O)CH(Me)CH(Et)CO_2H$,
$-C(O)CH(Me)CH(Et)CO_2Me$,
$-C(O)CH(Me)CH(Et)CO_2Et$,
$-C(O)CH(Me)CH(Et)CO_2iPr$,
$-C(O)CH(Me)CH(Et)CO_2tBu$,
-C(O)C(O)OH,

-C(O)C(O)NH_2,
-C(O)C(O)NHMe,
-C(O)C(O)NMe_2,
-C(O)NH_2,
-C(O)NMe_2,
-C(O)NH-CH_2-C(O)OH,
-C(O)NH-CH_2-C(O)OMe,
-C(O)NH-CH_2-C(O)OEt,
-C(O)NH-CH_2-C(O)OiPr,
-C(O)NH-CH_2-C(O)OtBu,
-C(O)NH-CH(Me)-C(O)OH,
-C(O)NH-CH(Me)-C(O)OMe,
-C(O)NH-CH(Me)-C(O)OEt,
-C(O)NH-CH(Me)-C(O)iPr,
-C(O)NH-CH(Me)-C(O)tBu,
-C(O)NH-CH(Et)-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OMe,
-C(O)NH-$C(Me)_2$-C(O)OEt,
-C(O)NH-$C(Me)_2$-C(O)iPr,
-C(O)NH-$C(Me)_2$-C(O)tBu,
-C(O)NH-CMe(Et)-C(O)OH,
-C(O)NH-CH(F)-C(O)OH,
-C(O)NH-CH(CF_3)-C(O)OH,
-C(O)NH-CH(OH)-C(O)OH,
-C(O)NH-CH(cyclopropyl)-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-CF(Me)-C(O)OH,
-C(O)NH-C(Me)(CF_3)-C(O)OH,
-C(O)NH-C(Me)(OH)-C(O)OH,
-C(O)NH-C(Me)(cyclopropyl)CO_2H,

-C(O)NMe-CH_2-C(O)OH,
-C(O)NMe-CH_2-C(O)OMe,
-C(O)NMe-CH_2-C(O)OEt,
-C(O)NMe-CH_2-C(O)OiPr,
-C(O)NMe-CH_2-C(O)tBu,
-C(O)NMe-CH(Me)-C(O)OH,
-C(O)NMe-CH(F)-C(O)OH,
-C(O)NMe-CH(CF_3)-C(O)OH,
-C(O)NMe-CH(OH)-C(O)OH,
-C(O)NMe-CH(cyclopropyl)-C(O)OH,
-C(O)NMe-C(Me)$_2$-C(O)OH,
-C(O)NMe-CF(Me)-C(O)OH,
-C(O)NMe-C(Me)(CF_3)-C(O)OH,
-C(O)NMe-C(Me)(OH)-C(O)OH,
-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH, or
-C(O)-N(Me)-5-tetrazolyl.

3. A compound represented by formula I or a pharmaceutically acceptable salt or a prodrug derivative thereof:



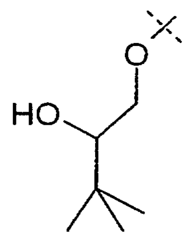
(I)

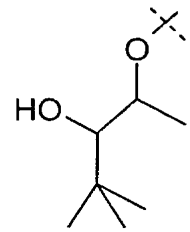
wherein;

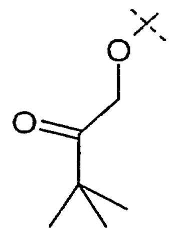
R and R' are independently methyl or ethyl;

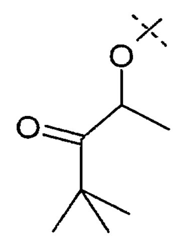
R_1 and R_2 are independently selected from the group consisting of hydrogen, fluoro, -Cl, -CF_3, -CH_2F, -CHF_2, methoxy, ethoxy, vinyl, methyl, or cyclopropyl;

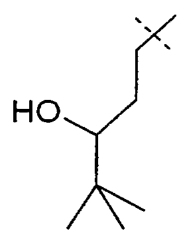
Z_B is a branched alkyl terminated selected from the formulae:

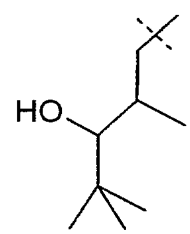
 ,

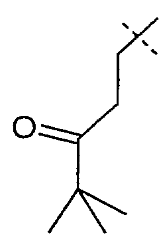
 ,

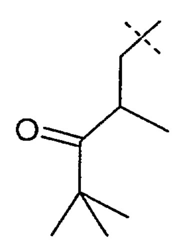


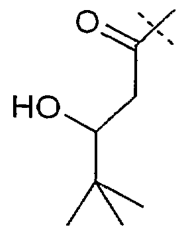
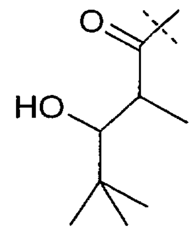
 ,

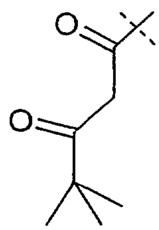
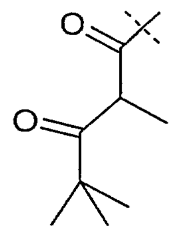
 ,

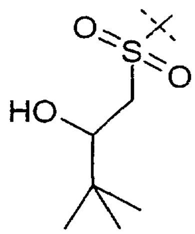
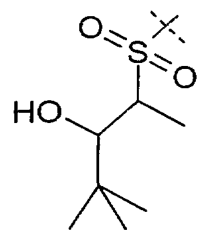
 ,

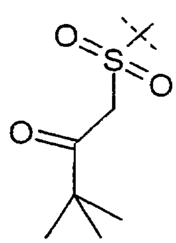
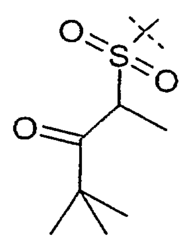


 ;

 ,  ,

  ,

 ,  ,

 , or  ;

Z_C is selected from

-C(O)NH_2,

-C(O)NMe_2,

-C(O)NH-CH_2-C(O)OH,
-C(O)NH-CH_2-C(O)OMe,
-C(O)NH-CH_2-C(O)OEt,
-C(O)NH-CH_2-C(O)OiPr,
-C(O)NH-CH_2-C(O)OtBu,
-C(O)NH-CH(Me)-C(O)OH,
-C(O)NH-CH(Me)-C(O)OMe,
-C(O)NH-CH(Me)-C(O)OEt,
-C(O)NH-CH(Me)-C(O)iPr,
-C(O)NH-CH(Me)-C(O)tBu,
-C(O)NH-CH(Et)-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OMe,
-C(O)NH-$C(Me)_2$-C(O)OEt,
-C(O)NH-$C(Me)_2$-C(O)iPr,
-C(O)NH-$C(Me)_2$-C(O)tBu,
-C(O)NH-CMe(Et)-C(O)OH,
-C(O)NH-CH(F)-C(O)OH,
-C(O)NH-CH(CF_3)-C(O)OH,
-C(O)NH-CH(OH)-C(O)OH,
-C(O)NH-CH(cyclopropyl)-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-$C(Me)_2$-C(O)OH,
-C(O)NH-CF(Me)-C(O)OH,
-C(O)NH-C(Me)(CF_3)-C(O)OH,
-C(O)NH-C(Me)(OH)-C(O)OH,
-C(O)NH-C(Me)(cyclopropyl)CO_2H,
-C(O)NMe-CH_2-C(O)OH,
-C(O)NMe-CH_2-C(O)OMe,
-C(O)NMe-CH_2-C(O)OEt,
-C(O)NMe-CH_2-C(O)OiPr,
-C(O)NMe-CH_2-C(O)tBu,

-C(O)NMe-CH(Me)-C(O)OH,

-C(O)NMe-CH(F)-C(O)OH,

-C(O)NMe-CH(CF_3)-C(O)OH,

-C(O)NMe-CH(OH)-C(O)OH,

-C(O)NMe-CH(cyclopropyl)-C(O)OH,

-C(O)NMe-C($Me)_2$-C(O)OH,

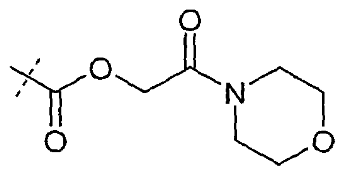
-C(O)NMe-CF(Me)-C(O)OH,

-C(O)NMe-C(Me)(CF_3)-C(O)OH,

-C(O)NMe-C(Me)(OH)-C(O)OH,

-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH,

-C(O)-N(Me)-5-tetrazolyl,



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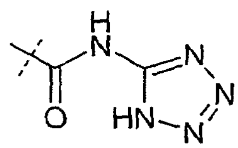

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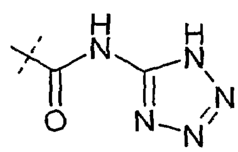
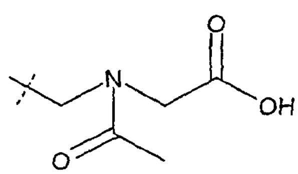


,or



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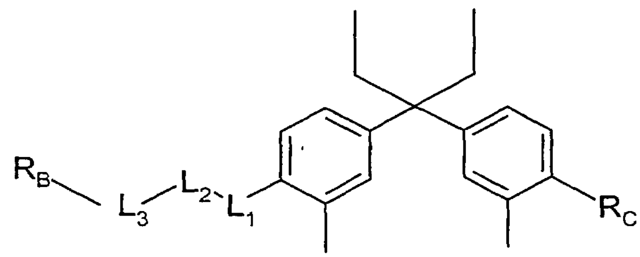
4. A compound or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



wherein;

said compound is selected from a compound code numbered 1 thru 468, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the horizontal line following the compound code number, as set out in the following Table 1 :

Table 1

No.	R_B	L_3	L_2	L_1	R_C
1	tBu	C(O)	CH2	O	CO2Me
2	tBu	CHOH	CH2	O	CO2Me
3	tBu	C(Me)OH	CH2	O	CO2Me
4	tBu	C(O)	CH(Me)	O	CO2Me
5	tBu	CHOH	CH(Me)	O	CO2Me
6	tBu	C(Me)OH	CH(Me)	O	CO2Me
7	tBu	C(O)	CH2	O	CO2H
8	tBu	CHOH	CH2	O	CO2H
9	tBu	C(Me)OH	CH2	O	CO2H
10	tBu	C(O)	CH(Me)	O	CO2H
11	tBu	CHOH	CH(Me)	O	CO2H
12	tBu	C(Me)OH	CH(Me)	O	CO2H
13	tBu	C(O)	CH2	O	C(O)NH2
14	tBu	CHOH	CH2	O	C(O)NH2
15	tBu	C(Me)OH	CH2	O	C(O)NH2
16	tBu	C(O)	CH(Me)	O	C(O)NH2
17	tBu	CHOH	CH(Me)	O	C(O)NH2
18	tBu	C(Me)OH	CH(Me)	O	C(O)NH2

19	tBu	C(O)	CH2	O	C(O)NMe2
20	tBu	CHOH	CH2	O	C(O)NMe2
21	tBu	C(Me)OH	CH2	O	C(O)NMe2
22	tBu	C(O)	CH(Me)	O	C(O)NMe2
23	tBu	CHOH	CH(Me)	O	C(O)NMe2
24	tBu	C(Me)OH	CH(Me)	O	C(O)NMe2
25	tBu	C(O)	CH2	O	5-tetrazolyl
26	tBu	CHOH	CH2	O	5-tetrazolyl
27	tBu	C(Me)OH	CH2	O	5-tetrazolyl
28	tBu	C(O)	CH(Me)	O	5-tetrazolyl
29	tBu	CHOH	CH(Me)	O	5-tetrazolyl
30	tBu	C(Me)OH	CH(Me)	O	5-tetrazolyl
31	tBu	C(O)	CH2	O	C(O)-NH-5-tetrazolyl
32	tBu	CHOH	CH2	O	C(O)-NH-5-tetrazolyl
33	tBu	C(Me)OH	CH2	O	C(O)-NH-5-tetrazolyl
34	tBu	C(O)	CH(Me)	O	C(O)-NH-5-tetrazolyl
35	tBu	CHOH	CH(Me)	O	C(O)-NH-5-tetrazolyl
36	tBu	C(Me)OH	CH(Me)	O	C(O)-NH-5-tetrazolyl
37	tBu	C(O)	CH2	O	C(O)NHCH2SO2Me
38	tBu	CHOH	CH2	O	C(O)NHCH2SO2Me
39	tBu	C(Me)OH	CH2	O	C(O)NHCH2SO2Me
40	tBu	C(O)	CH(Me)	O	C(O)NHCH2SO2Me
41	tBu	CHOH	CH(Me)	O	C(O)NHCH2SO2Me
42	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2SO2Me
43	tBu	C(O)	CH2	O	C(O)NHCH2S(O)Me
44	tBu	CHOH	CH2	O	C(O)NHCH2S(O)Me
45	tBu	C(Me)OH	CH2	O	C(O)NHCH2S(O)Me
46	tBu	C(O)	CH(Me)	O	C(O)NHCH2S(O)Me
47	tBu	CHOH	CH(Me)	O	C(O)NHCH2S(O)Me
48	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2S(O)Me
49	tBu	C(O)	CH2	O	C(O)NHCH2CH2SO2Me

50	tBu	CHOH	CH2	O	C(O)NHCH2CH2SO2Me
51	tBu	C(Me)OH	CH2	O	C(O)NHCH2CH2SO2Me
52	tBu	C(O)	CH(Me)	O	C(O)NHCH2CH2SO2Me
53	tBu	CHOH	CH(Me)	O	C(O)NHCH2CH2SO2Me
54	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2CH2SO2Me
55	tBu	C(O)	CH2	O	C(O)NHCH2CH2S(O)Me
56	tBu	CHOH	CH2	O	C(O)NHCH2CH2S(O)Me
57	tBu	C(Me)OH	CH2	O	C(O)NHCH2CH2S(O)Me
58	tBu	C(O)	CH(Me)	O	C(O)NHCH2CH2S(O)Me
59	tBu	CHOH	CH(Me)	O	C(O)NHCH2CH2S(O)Me
60	tBu	C(Me)OH	CH(Me)	O	C(O)NHCH2CH2S(O)Me
61	tBu	C(O)	CH2	O	C(O)NHSO2Me
62	tBu	CHOH	CH2	O	C(O)NHSO2Me
63	tBu	C(Me)OH	CH2	O	C(O)NHSO2Me
64	tBu	C(O)	CH(Me)	O	C(O)NHSO2Me
65	tBu	CHOH	CH(Me)	O	C(O)NHSO2Me
66	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2Me
67	tBu	C(O)	CH2	O	C(O)NHS(O)Me
68	tBu	CHOH	CH2	O	C(O)NHS(O)Me
69	tBu	C(Me)OH	CH2	O	C(O)NHS(O)Me
70	tBu	C(O)	CH(Me)	O	C(O)NHS(O)Me
71	tBu	CHOH	CH(Me)	O	C(O)NHS(O)Me
72	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)Me
73	tBu	C(O)	CH2	O	C(O)NHSO2Et
74	tBu	CHOH	CH2	O	C(O)NHSO2Et
75	tBu	C(Me)OH	CH2	O	C(O)NHSO2Et
76	tBu	C(O)	CH(Me)	O	C(O)NHSO2Et
77	tBu	CHOH	CH(Me)	O	C(O)NHSO2Et
78	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2Et
79	tBu	C(O)	CH2	O	C(O)NHS(O)Et
80	tBu	CHOH	CH2	O	C(O)NHS(O)Et

81	tBu	C(Me)OH	CH2	O	C(O)NHS(O)Et
82	tBu	C(O)	CH(Me)	O	C(O)NHS(O)Et
83	tBu	CHOH	CH(Me)	O	C(O)NHS(O)Et
84	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)Et
85	tBu	C(O)	CH2	O	C(O)NHSO2iPr
86	tBu	CHOH	CH2	O	C(O)NHSO2iPr
87	tBu	C(Me)OH	CH2	O	C(O)NHSO2iPr
88	tBu	C(O)	CH(Me)	O	C(O)NHSO2iPr
89	tBu	CHOH	CH(Me)	O	C(O)NHSO2iPr
90	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2iPr
91	tBu	C(O)	CH2	O	C(O)NHS(O)iPr
92	tBu	CHOH	CH2	O	C(O)NHS(O)iPr
93	tBu	C(Me)OH	CH2	O	C(O)NHS(O)iPr
94	tBu	C(O)	CH(Me)	O	C(O)NHS(O)iPr
95	tBu	CHOH	CH(Me)	O	C(O)NHS(O)iPr
96	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)iPr
97	tBu	C(O)	CH2	O	C(O)NHSO2tBu
98	tBu	CHOH	CH2	O	C(O)NHSO2tBu
99	tBu	C(Me)OH	CH2	O	C(O)NHSO2tBu
100	tBu	C(O)	CH(Me)	O	C(O)NHSO2tBu
101	tBu	CHOH	CH(Me)	O	C(O)NHSO2tBu
102	tBu	C(Me)OH	CH(Me)	O	C(O)NHSO2tBu
103	tBu	C(O)	CH2	O	C(O)NHS(O)tBu
104	tBu	CHOH	CH2	O	C(O)NHS(O)tBu
105	tBu	C(Me)OH	CH2	O	C(O)NHS(O)tBu
106	tBu	C(O)	CH(Me)	O	C(O)NHS(O)tBu
107	tBu	CHOH	CH(Me)	O	C(O)NHS(O)tBu
108	tBu	C(Me)OH	CH(Me)	O	C(O)NHS(O)tBu
109	tBu	C(O)	CH2	O	CH2NHSO2Me
110	tBu	CHOH	CH2	O	CH2NHSO2Me
111	tBu	C(Me)OH	CH2	O	CH2NHSO2Me

112	tBu	C(O)	CH(Me)	O	CH2NHSO2Me
113	tBu	CHOH	CH(Me)	O	CH2NHSO2Me
114	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2Me
115	tBu	C(O)	CH2	O	CH2NHS(O)Me
116	tBu	CHOH	CH2	O	CH2NHS(O)Me
117	tBu	C(Me)OH	CH2	O	CH2NHS(O)Me
118	tBu	C(O)	CH(Me)	O	CH2NHS(O)Me
119	tBu	CHOH	CH(Me)	O	CH2NHS(O)Me
120	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)Me
121	tBu	C(O)	CH2	O	CH2NHSO2Et
122	tBu	CHOH	CH2	O	CH2NHSO2Et
123	tBu	C(Me)OH	CH2	O	CH2NHSO2Et
124	tBu	C(O)	CH(Me)	O	CH2NHSO2Et
125	tBu	CHOH	CH(Me)	O	CH2NHSO2Et
126	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2Et
127	tBu	C(O)	CH2	O	CH2NHS(O)Et
128	tBu	CHOH	CH2	O	CH2NHS(O)Et
129	tBu	C(Me)OH	CH2	O	CH2NHS(O)Et
130	tBu	C(O)	CH(Me)	O	CH2NHS(O)Et
131	tBu	CHOH	CH(Me)	O	CH2NHS(O)Et
132	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)Et
133	tBu	C(O)	CH2	O	CH2NHSO2iPr
134	tBu	CHOH	CH2	O	CH2NHSO2iPr
135	tBu	C(Me)OH	CH2	O	CH2NHSO2iPr
136	tBu	C(O)	CH(Me)	O	CH2NHSO2iPr
137	tBu	CHOH	CH(Me)	O	CH2NHSO2iPr
138	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2iPr
139	tBu	C(O)	CH2	O	CH2NHS(O)iPr
140	tBu	CHOH	CH2	O	CH2NHS(O)iPr
141	tBu	C(Me)OH	CH2	O	CH2NHS(O)iPr
142	tBu	C(O)	CH(Me)	O	CH2NHS(O)iPr

143	tBu	CHOH	CH(Me)	O	CH2NHS(O)iPr
144	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)iPr
145	tBu	C(O)	CH2	O	CH2NHSO2tBu
146	tBu	CHOH	CH2	O	CH2NHSO2tBu
147	tBu	C(Me)OH	CH2	O	CH2NHSO2tBu
148	tBu	C(O)	CH(Me)	O	CH2NHSO2tBu
149	tBu	CHOH	CH(Me)	O	CH2NHSO2tBu
150	tBu	C(Me)OH	CH(Me)	O	CH2NHSO2tBu
151	tBu	C(O)	CH2	O	CH2NHS(O)tBu
152	tBu	CHOH	CH2	O	CH2NHS(O)tBu
153	tBu	C(Me)OH	CH2	O	CH2NHS(O)tBu
154	tBu	C(O)	CH(Me)	O	CH2NHS(O)tBu
155	tBu	CHOH	CH(Me)	O	CH2NHS(O)tBu
156	tBu	C(Me)OH	CH(Me)	O	CH2NHS(O)tBu
157	tBu	C(O)	CH2	O	CH2-N-pyrrolidin-2-one
158	tBu	CHOH	CH2	O	CH2-N-pyrrolidin-2-one
159	tBu	C(Me)OH	CH2	O	CH2-N-pyrrolidin-2-one
160	tBu	C(O)	CH(Me)	O	CH2-N-pyrrolidin-2-one
161	tBu	CHOH	CH(Me)	O	CH2-N-pyrrolidin-2-one
162	tBu	C(Me)OH	CH(Me)	O	CH2-N-pyrrolidin-2-one
163	tBu	C(O)	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
164	tBu	CHOH	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
165	tBu	C(Me)OH	CH2	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
166	tBu	C(O)	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
167	tBu	CHOH	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-yl)
168	tBu	C(Me)OH	CH(Me)	O	CH2-(1-methylpyrrolidin-2-one-3-

					yl)
169	tBu	C(O)	CH2	O	CH2CO2Me
170	tBu	CHOH	CH2	O	CH2CO2Me
171	tBu	C(Me)OH	CH2	O	CH2CO2Me
172	tBu	C(O)	CH(Me)	O	CH2CO2Me
173	tBu	CHOH	CH(Me)	O	CH2CO2Me
174	tBu	C(Me)OH	CH(Me)	O	CH2CO2Me
175	tBu	C(O)	CH2	O	CH2CO2H
176	tBu	CHOH	CH2	O	CH2CO2H
177	tBu	C(Me)OH	CH2	O	CH2CO2H
178	tBu	C(O)	CH(Me)	O	CH2CO2H
179	tBu	CHOH	CH(Me)	O	CH2CO2H
180	tBu	C(Me)OH	CH(Me)	O	CH2CO2H
181	tBu	C(O)	CH2	O	CH2C(O)NH2
182	tBu	CHOH	CH2	O	CH2C(O)NH2
183	tBu	C(Me)OH	CH2	O	CH2C(O)NH2
184	tBu	C(O)	CH(Me)	O	CH2C(O)NH2
185	tBu	CHOH	CH(Me)	O	CH2C(O)NH2
186	tBu	C(Me)OH	CH(Me)	O	CH2C(O)NH2
187	tBu	C(O)	CH2	O	CH2C(O)NMe2
188	tBu	CHOH	CH2	O	CH2C(O)NMe2
189	tBu	C(Me)OH	CH2	O	CH2C(O)NMe2
190	tBu	C(O)	CH(Me)	O	CH2C(O)NMe2
191	tBu	CHOH	CH(Me)	O	CH2C(O)NMe2
192	tBu	C(Me)OH	CH(Me)	O	CH2C(O)NMe2
193	tBu	C(O)	CH2	O	CH2C(O)-N-pyrrolidine
194	tBu	CHOH	CH2	O	CH2C(O)-N-pyrrolidine
195	tBu	C(Me)OH	CH2	O	CH2C(O)-N-pyrrolidine
196	tBu	C(O)	CH(Me)	O	CH2C(O)-N-pyrrolidine
197	tBu	CHOH	CH(Me)	O	CH2C(O)-N-pyrrolidine
198	tBu	C(Me)OH	CH(Me)	O	CH2C(O)-N-pyrrolidine

199	tBu	C(O)	CH2	O	CH2-5-tetrazolyl
200	tBu	CHOH	CH2	O	CH2-5-tetrazolyl
201	tBu	C(Me)OH	CH2	O	CH2-5-tetrazolyl
202	tBu	C(O)	CH(Me)	O	CH2-5-tetrazolyl
203	tBu	CHOH	CH(Me)	O	CH2-5-tetrazolyl
204	tBu	C(Me)OH	CH(Me)	O	CH2-5-tetrazolyl
205	tBu	C(O)	CH2	O	C(O)C(O)OH
206	tBu	CHOH	CH2	O	C(O)C(O)OH
207	tBu	C(Me)OH	CH2	O	C(O)C(O)OH
208	tBu	C(O)	CH(Me)	O	C(O)C(O)OH
209	tBu	CHOH	CH(Me)	O	C(O)C(O)OH
210	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)OH
211	tBu	C(O)	CH2	O	CH(OH)C(O)OH
212	tBu	CHOH	CH2	O	CH(OH)C(O)OH
213	tBu	C(Me)OH	CH2	O	CH(OH)C(O)OH
214	tBu	C(O)	CH(Me)	O	CH(OH)C(O)OH
215	tBu	CHOH	CH(Me)	O	CH(OH)C(O)OH
216	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)OH
217	tBu	C(O)	CH2	O	C(O)C(O)NH2
218	tBu	CHOH	CH2	O	C(O)C(O)NH2
219	tBu	C(Me)OH	CH2	O	C(O)C(O)NH2
220	tBu	C(O)	CH(Me)	O	C(O)C(O)NH2
221	tBu	CHOH	CH(Me)	O	C(O)C(O)NH2
222	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)NH2
223	tBu	C(O)	CH2	O	CH(OH)C(O)NH2
224	tBu	CHOH	CH2	O	CH(OH)C(O)NH2
225	tBu	C(Me)OH	CH2	O	CH(OH)C(O)NH2
226	tBu	C(O)	CH(Me)	O	CH(OH)C(O)NH2
227	tBu	CHOH	CH(Me)	O	CH(OH)C(O)NH2
228	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)NH2
229	tBu	C(O)	CH2	O	C(O)C(O)NMe2

230	tBu	CHOH	CH2	O	C(O)C(O)NMe2
231	tBu	C(Me)OH	CH2	O	C(O)C(O)NMe2
232	tBu	C(O)	CH(Me)	O	C(O)C(O)NMe2
233	tBu	CHOH	CH(Me)	O	C(O)C(O)NMe2
234	tBu	C(Me)OH	CH(Me)	O	C(O)C(O)NMe2
235	tBu	C(O)	CH2	O	CH(OH)C(O)NMe2
236	tBu	CHOH	CH2	O	CH(OH)C(O)NMe2
237	tBu	C(Me)OH	CH2	O	CH(OH)C(O)NMe2
238	tBu	C(O)	CH(Me)	O	CH(OH)C(O)NMe2
239	tBu	CHOH	CH(Me)	O	CH(OH)C(O)NMe2
240	tBu	C(Me)OH	CH(Me)	O	CH(OH)C(O)NMe2
241	tBu	C(O)	CH2	O	CH2CH2CO2H
242	tBu	CHOH	CH2	O	CH2CH2CO2H
243	tBu	C(Me)OH	CH2	O	CH2CH2CO2H
244	tBu	C(O)	CH(Me)	O	CH2CH2CO2H
245	tBu	CHOH	CH(Me)	O	CH2CH2CO2H
246	tBu	C(Me)OH	CH(Me)	O	CH2CH2CO2H
247	tBu	C(O)	CH2	O	CH2CH2C(O)NH2
248	tBu	CHOH	CH2	O	CH2CH2C(O)NH2
249	tBu	C(Me)OH	CH2	O	CH2CH2C(O)NH2
250	tBu	C(O)	CH(Me)	O	CH2CH2C(O)NH2
251	tBu	CHOH	CH(Me)	O	CH2CH2C(O)NH2
252	tBu	C(Me)OH	CH(Me)	O	CH2CH2C(O)NH2
253	tBu	C(O)	CH2	O	CH2CH2C(O)NMe2
254	tBu	CHOH	CH2	O	CH2CH2C(O)NMe2
255	tBu	C(Me)OH	CH2	O	CH2CH2C(O)NMe2
256	tBu	C(O)	CH(Me)	O	CH2CH2C(O)NMe2
257	tBu	CHOH	CH(Me)	O	CH2CH2C(O)NMe2
258	tBu	C(Me)OH	CH(Me)	O	CH2CH2C(O)NMe2
259	tBu	C(O)	CH2	O	CH2CH2-5-tetrazolyl
260	tBu	CHOH	CH2	O	CH2CH2-5-tetrazolyl

261	tBu	C(Me)OH	CH2	O	CH2CH2-5-tetrazolyl
262	tBu	C(O)	CH(Me)	O	CH2CH2-5-tetrazolyl
263	tBu	CHOH	CH(Me)	O	CH2CH2-5-tetrazolyl
264	tBu	C(Me)OH	CH(Me)	O	CH2CH2-5-tetrazolyl
265	tBu	C(O)	CH2	O	CH2S(O)2Me
266	tBu	CHOH	CH2	O	CH2S(O)2Me
267	tBu	C(Me)OH	CH2	O	CH2S(O)2Me
268	tBu	C(O)	CH(Me)	O	CH2S(O)2Me
269	tBu	CHOH	CH(Me)	O	CH2S(O)2Me
270	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2Me
271	tBu	C(O)	CH2	O	CH2S(O)Me
272	tBu	CHOH	CH2	O	CH2S(O2Me
273	tBu	C(Me)OH	CH2	O	CH2S(O)Me
274	tBu	C(O)	CH(Me)	O	CH2S(O)Me
275	tBu	CHOH	CH(Me)	O	CH2S(O)Me
276	tBu	C(Me)OH	CH(Me)	O	CH2S(O)Me
277	tBu	C(O)	CH2	O	CH2CH2S(O)2Me
278	tBu	CHOH	CH2	O	CH2CH2S(O)2Me
279	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2Me
280	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2Me
281	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2Me
282	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2Me
283	tBu	C(O)	CH2	O	CH2CH2S(O)Me
284	tBu	CHOH	CH2	O	CH2CH2S(O)Me
285	tBu	C(Me)OH	CH2	O	CH2CH2S(O)Me
286	tBu	C(O)	CH(Me)	O	CH2CH2S(O)Me
287	tBu	CHOH	CH(Me)	O	CH2CH2S(O)Me
288	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)Me
289	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2Me
290	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2Me
291	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2Me

292	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2Me
293	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2Me
294	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2Me
295	tBu	C(O)	CH2	O	CH2CH2CH2S(O)Me
296	tBu	CHOH	CH2	O	CH2CH2CH2S(O)Me
297	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)Me
298	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)Me
299	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)Me
300	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)Me
301	tBu	C(O)	CH2	O	CH2S(O)2Et
302	tBu	CHOH	CH2	O	CH2S(O)2Et
303	tBu	C(Me)OH	CH2	O	CH2S(O)2Et
304	tBu	C(O)	CH(Me)	O	CH2S(O)2Et
305	tBu	CHOH	CH(Me)	O	CH2S(O)2Et
306	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2Et
307	tBu	C(O)	CH2	O	CH2S(O)Et
308	tBu	CHOH	CH2	O	CH2S(O)Et
309	tBu	C(Me)OH	CH2	O	CH2S(O)Et
310	tBu	C(O)	CH(Me)	O	CH2S(O)Et
311	tBu	CHOH	CH(Me)	O	CH2S(O)Et
312	tBu	C(Me)OH	CH(Me)	O	CH2S(O)Et
313	tBu	C(O)	CH2	O	CH2CH2S(O)2Et
314	tBu	CHOH	CH2	O	CH2CH2S(O)2Et
315	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2Et
316	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2Et
317	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2Et
318	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2Et
319	tBu	C(O)	CH2	O	CH2CH2S(O)Et
320	tBu	CHOH	CH2	O	CH2CH2S(O)Et
321	tBu	C(Me)OH	CH2	O	CH2CH2S(O)Et
322	tBu	C(O)	CH(Me)	O	CH2CH2S(O)Et

323	tBu	CHOH	CH(Me)	O	CH2CH2S(O)Et
324	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)Et
325	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2Et
326	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2Et
327	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2Et
328	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2Et
329	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2Et
330	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2Et
331	tBu	C(O)	CH2	O	CH2CH2CH2S(O)Et
332	tBu	CHOH	CH2	O	CH2CH2CH2S(O)Et
333	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)Et
334	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)Et
335	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)Et
336	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)Et
337	tBu	C(O)	CH2	O	CH2S(O)2iPr
338	tBu	CHOH	CH2	O	CH2S(O)2iPr
339	tBu	C(Me)OH	CH2	O	CH2S(O)2iPr
340	tBu	C(O)	CH(Me)	O	CH2S(O)2iPr
341	tBu	CHOH	CH(Me)	O	CH2S(O)2iPr
342	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2iPr
343	tBu	C(O)	CH2	O	CH2S(O)iPr
344	tBu	CHOH	CH2	O	CH2S(O)iPr
345	tBu	C(Me)OH	CH2	O	CH2S(O)iPr
346	tBu	C(O)	CH(Me)	O	CH2S(O)iPr
347	tBu	CHOH	CH(Me)	O	CH2S(O)iPr
348	tBu	C(Me)OH	CH(Me)	O	CH2S(O)iPr
349	tBu	C(O)	CH2	O	CH2CH2S(O)2iPr
350	tBu	CHOH	CH2	O	CH2CH2S(O)2iPr
351	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2iPr
352	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2iPr
353	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2iPr

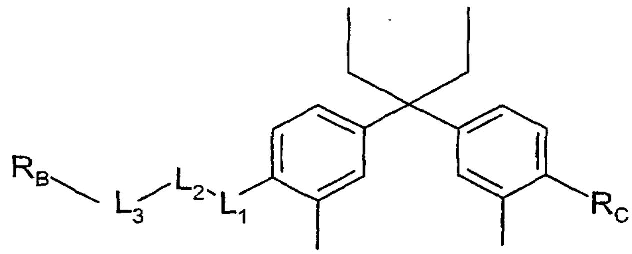
354	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2iPr
355	tBu	C(O)	CH2	O	CH2CH2S(O)iPr
356	tBu	CHOH	CH2	O	CH2CH2S(O)iPr
357	tBu	C(Me)OH	CH2	O	CH2CH2S(O)iPr
358	tBu	C(O)	CH(Me)	O	CH2CH2S(O)iPr
359	tBu	CHOH	CH(Me)	O	CH2CH2S(O)iPr
360	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)iPr
361	tBu	C(O)	CH2	O	CH2S(O)2tBu
362	tBu	CHOH	CH2	O	CH2S(O)2tBu
363	tBu	C(Me)OH	CH2	O	CH2S(O)2tBu
364	tBu	C(O)	CH(Me)	O	CH2S(O)2tBu
365	tBu	CHOH	CH(Me)	O	CH2S(O)2tBu
366	tBu	C(Me)OH	CH(Me)	O	CH2S(O)2tBu
367	tBu	C(O)	CH2	O	CH2S(O)tBu
368	tBu	CHOH	CH2	O	CH2S(O)tBu
369	tBu	C(Me)OH	CH2	O	CH2S(O)tBu
370	tBu	C(O)	CH(Me)	O	CH2S(O)tBu
371	tBu	CHOH	CH(Me)	O	CH2S(O)tBu
372	tBu	C(Me)OH	CH(Me)	O	CH2S(O)tBu
373	tBu	C(O)	CH2	O	CH2CH2S(O)2tBu
374	tBu	CHOH	CH2	O	CH2CH2S(O)2tBu
375	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2tBu
376	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2tBu
377	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2tBu
378	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2tBu
379	tBu	C(O)	CH2	O	CH2CH2S(O)tBu
380	tBu	CHOH	CH2	O	CH2CH2S(O)tBu
381	tBu	C(Me)OH	CH2	O	CH2CH2S(O)tBu
382	tBu	C(O)	CH(Me)	O	CH2CH2S(O)tBu
383	tBu	CHOH	CH(Me)	O	CH2CH2S(O)tBu
384	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)tBu

385	tBu	C(O)	CH2	O	CH2CH2S(O)2NH2
386	tBu	CHOH	CH2	O	CH2CH2S(O)2NH2
387	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2NH2
388	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2NH2
389	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2NH2
390	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2NH2
391	tBu	C(O)	CH2	O	CH2CH2S(O)NH2
392	tBu	CHOH	CH2	O	CH2CH2S(O)NH2
393	tBu	C(Me)OH	CH2	O	CH2CH2S(O)NH2
394	tBu	C(O)	CH(Me)	O	CH2CH2S(O)NH2
395	tBu	CHOH	CH(Me)	O	CH2CH2S(O)NH2
396	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)NH2
397	tBu	C(O)	CH2	O	CH2CH2S(O)2NMe2
398	tBu	CHOH	CH2	O	CH2CH2S(O)2NMe2
399	tBu	C(Me)OH	CH2	O	CH2CH2S(O)2NMe2
400	tBu	C(O)	CH(Me)	O	CH2CH2S(O)2NMe2
401	tBu	CHOH	CH(Me)	O	CH2CH2S(O)2NMe2
402	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)2NMe2
403	tBu	C(O)	CH2	O	CH2CH2S(O)NMe2
404	tBu	CHOH	CH2	O	CH2CH2S(O)NMe2
405	tBu	C(Me)OH	CH2	O	CH2CH2S(O)NMe2
406	tBu	C(O)	CH(Me)	O	CH2CH2S(O)NMe2
407	tBu	CHOH	CH(Me)	O	CH2CH2S(O)NMe2
408	tBu	C(Me)OH	CH(Me)	O	CH2CH2S(O)NMe2
409	tBu	C(O)	CH2	O	C(O)CH2S(O)2Me
410	tBu	CHOH	CH2	O	C(O)CH2S(O)2Me
411	tBu	C(Me)OH	CH2	O	C(O)CH2S(O)2Me
412	tBu	C(O)	CH(Me)	O	C(O)CH2S(O)2Me
413	tBu	CHOH	CH(Me)	O	C(O)CH2S(O)2Me
414	tBu	C(Me)OH	CH(Me)	O	C(O)CH2S(O)2Me
415	tBu	C(O)	CH2	O	C(O)CH2S(O)Me

416	tBu	CHOH	CH2	O	C(O)CH2S(O)Me
417	tBu	C(Me)OH	CH2	O	C(O)CH2S(O)Me
418	tBu	C(O)	CH(Me)	O	C(O)CH2S(O)Me
419	tBu	CHOH	CH(Me)	O	C(O)CH2S(O)Me
420	tBu	C(Me)OH	CH(Me)	O	C(O)CH2S(O)Me
421	tBu	C(O)	CH2	O	C(O)CH2CH2S(O)2Me
422	tBu	CHOH	CH2	O	C(O)CH2CH2S(O)2Me
423	tBu	C(Me)OH	CH2	O	C(O)CH2CH2S(O)2Me
424	tBu	C(O)	CH(Me)	O	C(O)CH2CH2S(O)2Me
425	tBu	CHOH	CH(Me)	O	C(O)CH2CH2S(O)2Me
426	tBu	C(Me)OH	CH(Me)	O	C(O)CH2CH2S(O)2Me
427	tBu	C(O)	CH2	O	C(O)CH2CH2S(O)Me
428	tBu	CHOH	CH2	O	C(O)CH2CH2S(O)Me
429	tBu	C(Me)OH	CH2	O	C(O)CH2CH2S(O)Me
430	tBu	C(O)	CH(Me)	O	C(O)CH2CH2S(O)Me
431	tBu	CHOH	CH(Me)	O	C(O)CH2CH2S(O)Me
432	tBu	C(Me)OH	CH(Me)	O	C(O)CH2CH2S(O)Me
433	tBu	C(O)	CH2	O	CH2CH2CH2S(O)2NH2
434	tBu	CHOH	CH2	O	CH2CH2CH2S(O)2NH2
435	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)2NH2
436	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)2NH2
437	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)2NH2
438	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)2NH2
439	tBu	C(O)	CH2	O	CH2CH2CH2S(O)NH2
440	tBu	CHOH	CH2	O	CH2CH2CH2S(O)NH2
441	tBu	C(Me)OH	CH2	O	CH2CH2CH2S(O)NH2
442	tBu	C(O)	CH(Me)	O	CH2CH2CH2S(O)NH2
443	tBu	CHOH	CH(Me)	O	CH2CH2CH2S(O)NH2
444	tBu	C(Me)OH	CH(Me)	O	CH2CH2CH2S(O)NH2
445	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
446	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl

447	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
448	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
449	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
450	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
451	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
452	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
453	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
454	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
455	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
456	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
457	tBu	C(O)	CH2	CH2	imidazolidine-2,4-dione-5-yl
458	tBu	CHOH	CH2	CH2	imidazolidine-2,4-dione-5-yl
459	tBu	C(Me)OH	CH2	CH2	imidazolidine-2,4-dione-5-yl
460	tBu	C(O)	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
461	tBu	CHOH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
462	tBu	C(Me)OH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
463	tBu	C(O)	CH2	CH2	isoxazol-3-ol-5-yl
464	tBu	CHOH	CH2	CH2	isoxazol-3-ol-5-yl
465	tBu	C(Me)OH	CH2	CH2	isoxazol-3-ol-5-yl
466	tBu	C(O)	CH(Me)	CH2	isoxazol-3-ol-5-yl
467	tBu	CHOH	CH(Me)	CH2	isoxazol-3-ol-5-yl
468	tBu	C(Me)OH	CH(Me)	CH2	isoxazol-3-ol-5-yl

5. A compound or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



said compound is selected from a compound code numbered 1A thru 468A, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the row following the compound code number, as set out in the following Table 2 :

Table 2

	R_B	L_3	L_2	L_1	R_C
1A	tBu	C(O)	CH2	CH2	CO2Me
2A	tBu	CHOH	CH2	CH2	CO2Me
3A	tBu	C(Me)OH	CH2	CH2	CO2Me
4A	tBu	C(O)	CH(Me)	CH2	CO2Me
5A	tBu	CHOH	CH(Me)	CH2	CO2Me
6A	tBu	C(Me)OH	CH(Me)	CH2	CO2Me
7A	tBu	C(O)	CH2	CH2	CO2H
8A	tBu	CHOH	CH2	CH2	CO2H
9A	tBu	C(Me)OH	CH2	CH2	CO2H
10A	tBu	C(O)	CH(Me)	CH2	CO2H
11A	tBu	CHOH	CH(Me)	CH2	CO2H
12A	tBu	C(Me)OH	CH(Me)	CH2	CO2H
13A	tBu	C(O)	CH2	CH2	C(O)NH2
14A	tBu	CHOH	CH2	CH2	C(O)NH2
15A	tBu	C(Me)OH	CH2	CH2	C(O)NH2
16A	tBu	C(O)	CH(Me)	CH2	C(O)NH2
17A	tBu	CHOH	CH(Me)	CH2	C(O)NH2
18A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NH2
19A	tBu	C(O)	CH2	CH2	C(O)NMe2
20A	tBu	CHOH	CH2	CH2	C(O)NMe2
21A	tBu	C(Me)OH	CH2	CH2	C(O)NMe2

22A	tBu	C(O)	CH(Me)	CH2	C(O)NMe2
23A	tBu	CHOH	CH(Me)	CH2	C(O)NMe2
24A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NMe2
25A	tBu	C(O)	CH2	CH2	5-tetrazolyl
26A	tBu	CHOH	CH2	CH2	5-tetrazolyl
27A	tBu	C(Me)OH	CH2	CH2	5-tetrazolyl
28A	tBu	C(O)	CH(Me)	CH2	5-tetrazolyl
29A	tBu	CHOH	CH(Me)	CH2	5-tetrazolyl
30A	tBu	C(Me)OH	CH(Me)	CH2	5-tetrazolyl
31A	tBu	C(O)	CH2	CH2	C(O)-NH-5-tetrazolyl
32A	tBu	CHOH	CH2	CH2	C(O)-NH-5-tetrazolyl
33A	tBu	C(Me)OH	CH2	CH2	C(O)-NH-5-tetrazolyl
34A	tBu	C(O)	CH(Me)	CH2	C(O)-NH-5-tetrazolyl
35A	tBu	CHOH	CH(Me)	CH2	C(O)-NH-5-tetrazolyl
36A	tBu	C(Me)OH	CH(Me)	CH2	C(O)-NH-5-tetrazolyl
37A	tBu	C(O)	CH2	CH2	C(O)NHCH2SO2Me
38A	tBu	CHOH	CH2	CH2	C(O)NHCH2SO2Me
39A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2SO2Me
40A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2SO2Me
41A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2SO2Me
42A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2SO2Me
43A	tBu	C(O)	CH2	CH2	C(O)NHCH2S(O)Me
44A	tBu	CHOH	CH2	CH2	C(O)NHCH2S(O)Me
45A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2S(O)Me
46A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2S(O)Me
47A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2S(O)Me
48A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2S(O)Me
49A	tBu	C(O)	CH2	CH2	C(O)NHCH2CH2SO2Me
50A	tBu	CHOH	CH2	CH2	C(O)NHCH2CH2SO2Me
51A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2CH2SO2Me
52A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2CH2SO2Me

53A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2CH2SO2Me
54A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2CH2SO2Me
55A	tBu	C(O)	CH2	CH2	C(O)NHCH2CH2S(O)Me
56A	tBu	CHOH	CH2	CH2	C(O)NHCH2CH2S(O)Me
57A	tBu	C(Me)OH	CH2	CH2	C(O)NHCH2CH2S(O)Me
58A	tBu	C(O)	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
59A	tBu	CHOH	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
60A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHCH2CH2S(O)Me
61A	tBu	C(O)	CH2	CH2	C(O)NHSO2Me
62A	tBu	CHOH	CH2	CH2	C(O)NHSO2Me
63A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2Me
64A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2Me
65A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2Me
66A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2Me
67A	tBu	C(O)	CH2	CH2	C(O)NHS(O)Me
68A	tBu	CHOH	CH2	CH2	C(O)NHS(O)Me
69A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)Me
70A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)Me
71A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)Me
72A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)Me
73A	tBu	C(O)	CH2	CH2	C(O)NHSO2Et
74A	tBu	CHOH	CH2	CH2	C(O)NHSO2Et
75A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2Et
76A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2Et
77A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2Et
78A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2Et
79A	tBu	C(O)	CH2	CH2	C(O)NHS(O)Et
80A	tBu	CHOH	CH2	CH2	C(O)NHS(O)Et
81A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)Et
82A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)Et
83A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)Et

84A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)Et
85A	tBu	C(O)	CH2	CH2	C(O)NHSO2iPr
86A	tBu	CHOH	CH2	CH2	C(O)NHSO2iPr
87A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2iPr
88A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2iPr
89A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2iPr
90A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2iPr
91A	tBu	C(O)	CH2	CH2	C(O)NHS(O)iPr
92A	tBu	CHOH	CH2	CH2	C(O)NHS(O)iPr
93A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)iPr
94A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)iPr
95A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)iPr
96A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)iPr
97A	tBu	C(O)	CH2	CH2	C(O)NHSO2tBu
98A	tBu	CHOH	CH2	CH2	C(O)NHSO2tBu
99A	tBu	C(Me)OH	CH2	CH2	C(O)NHSO2tBu
100A	tBu	C(O)	CH(Me)	CH2	C(O)NHSO2tBu
101A	tBu	CHOH	CH(Me)	CH2	C(O)NHSO2tBu
102A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHSO2tBu
103A	tBu	C(O)	CH2	CH2	C(O)NHS(O)tBu
104A	tBu	CHOH	CH2	CH2	C(O)NHS(O)tBu
105A	tBu	C(Me)OH	CH2	CH2	C(O)NHS(O)tBu
106A	tBu	C(O)	CH(Me)	CH2	C(O)NHS(O)tBu
107A	tBu	CHOH	CH(Me)	CH2	C(O)NHS(O)tBu
108A	tBu	C(Me)OH	CH(Me)	CH2	C(O)NHS(O)tBu
109A	tBu	C(O)	CH2	CH2	CH2NHSO2Me
110A	tBu	CHOH	CH2	CH2	CH2NHSO2Me
111A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2Me
112A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2Me
113A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2Me
114A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2Me

115A	tBu	C(O)	CH2	CH2	CH2NHS(O)Me
116A	tBu	CHOH	CH2	CH2	CH2NHS(O)Me
117A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)Me
118A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)Me
119A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)Me
120A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)Me
121A	tBu	C(O)	CH2	CH2	CH2NHSO2Et
122A	tBu	CHOH	CH2	CH2	CH2NHSO2Et
123A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2Et
124A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2Et
125A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2Et
126A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2Et
127A	tBu	C(O)	CH2	CH2	CH2NHS(O)Et
128A	tBu	CHOH	CH2	CH2	CH2NHS(O)Et
129A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)Et
130A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)Et
131A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)Et
132A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)Et
133A	tBu	C(O)	CH2	CH2	CH2NHSO2iPr
134A	tBu	CHOH	CH2	CH2	CH2NHSO2iPr
135A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2iPr
136A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2iPr
137A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2iPr
138A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2iPr
139A	tBu	C(O)	CH2	CH2	CH2NHS(O)iPr
140A	tBu	CHOH	CH2	CH2	CH2NHS(O)iPr
141A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)iPr
142A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)iPr
143A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)iPr
144A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)iPr
145A	tBu	C(O)	CH2	CH2	CH2NHSO2tBu

146A	tBu	CHOH	CH2	CH2	CH2NHSO2tBu
147A	tBu	C(Me)OH	CH2	CH2	CH2NHSO2tBu
148A	tBu	C(O)	CH(Me)	CH2	CH2NHSO2tBu
149A	tBu	CHOH	CH(Me)	CH2	CH2NHSO2tBu
150A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHSO2tBu
151A	tBu	C(O)	CH2	CH2	CH2NHS(O)tBu
152A	tBu	CHOH	CH2	CH2	CH2NHS(O)tBu
153A	tBu	C(Me)OH	CH2	CH2	CH2NHS(O)tBu
154A	tBu	C(O)	CH(Me)	CH2	CH2NHS(O)tBu
155A	tBu	CHOH	CH(Me)	CH2	CH2NHS(O)tBu
156A	tBu	C(Me)OH	CH(Me)	CH2	CH2NHS(O)tBu
157A	tBu	C(O)	CH2	CH2	CH2-N-pyrrolidin-2-one
158A	tBu	CHOH	CH2	CH2	CH2-N-pyrrolidin-2-one
159A	tBu	C(Me)OH	CH2	CH2	CH2-N-pyrrolidin-2-one
160A	tBu	C(O)	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
161A	tBu	CHOH	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
162A	tBu	C(Me)OH	CH(Me)	CH2	CH2-N-pyrrolidin-2-one
163A	tBu	C(O)	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
164A	tBu	CHOH	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
165A	tBu	C(Me)OH	CH2	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
166A	tBu	C(O)	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
167A	tBu	CHOH	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
168A	tBu	C(Me)OH	CH(Me)	CH2	CH2-(1-methylpyrrolidin-2-one-3-yl)
169A	tBu	C(O)	CH2	CH2	CH2CO2Me
170A	tBu	CHOH	CH2	CH2	CH2CO2Me

171A	tBu	C(Me)OH	CH2	CH2	CH2CO2Me
172A	tBu	C(O)	CH(Me)	CH2	CH2CO2Me
173A	tBu	CHOH	CH(Me)	CH2	CH2CO2Me
174A	tBu	C(Me)OH	CH(Me)	CH2	CH2CO2Me
175A	tBu	C(O)	CH2	CH2	CH2CO2H
176A	tBu	CHOH	CH2	CH2	CH2CO2H
177A	tBu	C(Me)OH	CH2	CH2	CH2CO2H
178A	tBu	C(O)	CH(Me)	CH2	CH2CO2H
179A	tBu	CHOH	CH(Me)	CH2	CH2CO2H
180A	tBu	C(Me)OH	CH(Me)	CH2	CH2CO2H
181A	tBu	C(O)	CH2	CH2	CH2C(O)NH2
182A	tBu	CHOH	CH2	CH2	CH2C(O)NH2
183A	tBu	C(Me)OH	CH2	CH2	CH2C(O)NH2
184A	tBu	C(O)	CH(Me)	CH2	CH2C(O)NH2
185A	tBu	CHOH	CH(Me)	CH2	CH2C(O)NH2
186A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)NH2
187A	tBu	C(O)	CH2	CH2	CH2C(O)NMe2
188A	tBu	CHOH	CH2	CH2	CH2C(O)NMe2
189A	tBu	C(Me)OH	CH2	CH2	CH2C(O)NMe2
190A	tBu	C(O)	CH(Me)	CH2	CH2C(O)NMe2
191A	tBu	CHOH	CH(Me)	CH2	CH2C(O)NMe2
192A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)NMe2
193A	tBu	C(O)	CH2	CH2	CH2C(O)-N-pyrrolidine
194A	tBu	CHOH	CH2	CH2	CH2C(O)-N-pyrrolidine
195A	tBu	C(Me)OH	CH2	CH2	CH2C(O)-N-pyrrolidine
196A	tBu	C(O)	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
197A	tBu	CHOH	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
198A	tBu	C(Me)OH	CH(Me)	CH2	CH2C(O)-N-pyrrolidine
199A	tBu	C(O)	CH2	CH2	CH2-5-tetrazolyl
200A	tBu	CHOH	CH2	CH2	CH2-5-tetrazolyl
201A	tBu	C(Me)OH	CH2	CH2	CH2-5-tetrazolyl

202A	tBu	C(O)	CH(Me)	CH2	CH2-5-tetrazolyl
203A	tBu	CHOH	CH(Me)	CH2	CH2-5-tetrazolyl
204A	tBu	C(Me)OH	CH(Me)	CH2	CH2-5-tetrazolyl
205A	tBu	C(O)	CH2	CH2	C(O)C(O)OH
206A	tBu	CHOH	CH2	CH2	C(O)C(O)OH
207A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)OH
208A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)OH
209A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)OH
210A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)OH
211A	tBu	C(O)	CH2	CH2	CH(OH)C(O)OH
212A	tBu	CHOH	CH2	CH2	CH(OH)C(O)OH
213A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)OH
214A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)OH
215A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)OH
216A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)OH
217A	tBu	C(O)	CH2	CH2	C(O)C(O)NH2
218A	tBu	CHOH	CH2	CH2	C(O)C(O)NH2
219A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)NH2
220A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)NH2
221A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)NH2
222A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)NH2
223A	tBu	C(O)	CH2	CH2	CH(OH)C(O)NH2
224A	tBu	CHOH	CH2	CH2	CH(OH)C(O)NH2
225A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)NH2
226A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)NH2
227A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)NH2
228A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)NH2
229A	tBu	C(O)	CH2	CH2	C(O)C(O)NMe2
230A	tBu	CHOH	CH2	CH2	C(O)C(O)NMe2
231A	tBu	C(Me)OH	CH2	CH2	C(O)C(O)NMe2
232A	tBu	C(O)	CH(Me)	CH2	C(O)C(O)NMe2

233A	tBu	CHOH	CH(Me)	CH2	C(O)C(O)NMe2
234A	tBu	C(Me)OH	CH(Me)	CH2	C(O)C(O)NMe2
235A	tBu	C(O)	CH2	CH2	CH(OH)C(O)NMe2
236A	tBu	CHOH	CH2	CH2	CH(OH)C(O)NMe2
237A	tBu	C(Me)OH	CH2	CH2	CH(OH)C(O)NMe2
238A	tBu	C(O)	CH(Me)	CH2	CH(OH)C(O)NMe2
239A	tBu	CHOH	CH(Me)	CH2	CH(OH)C(O)NMe2
240A	tBu	C(Me)OH	CH(Me)	CH2	CH(OH)C(O)NMe2
241A	tBu	C(O)	CH2	CH2	CH2CH2CO2H
242A	tBu	CHOH	CH2	CH2	CH2CH2CO2H
243A	tBu	C(Me)OH	CH2	CH2	CH2CH2CO2H
244A	tBu	C(O)	CH(Me)	CH2	CH2CH2CO2H
245A	tBu	CHOH	CH(Me)	CH2	CH2CH2CO2H
246A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CO2H
247A	tBu	C(O)	CH2	CH2	CH2CH2C(O)NH2
248A	tBu	CHOH	CH2	CH2	CH2CH2C(O)NH2
249A	tBu	C(Me)OH	CH2	CH2	CH2CH2C(O)NH2
250A	tBu	C(O)	CH(Me)	CH2	CH2CH2C(O)NH2
251A	tBu	CHOH	CH(Me)	CH2	CH2CH2C(O)NH2
252A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2C(O)NH2
253A	tBu	C(O)	CH2	CH2	CH2CH2C(O)NMe2
254A	tBu	CHOH	CH2	CH2	CH2CH2C(O)NMe2
255A	tBu	C(Me)OH	CH2	CH2	CH2CH2C(O)NMe2
256A	tBu	C(O)	CH(Me)	CH2	CH2CH2C(O)NMe2
257A	tBu	CHOH	CH(Me)	CH2	CH2CH2C(O)NMe2
258A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2C(O)NMe2
259A	tBu	C(O)	CH2	CH2	CH2CH2-5-tetrazolyl
260A	tBu	CHOH	CH2	CH2	CH2CH2-5-tetrazolyl
261A	tBu	C(Me)OH	CH2	CH2	CH2CH2-5-tetrazolyl
262A	tBu	C(O)	CH(Me)	CH2	CH2CH2-5-tetrazolyl
263A	tBu	CHOH	CH(Me)	CH2	CH2CH2-5-tetrazolyl

264A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2-5-tetrazolyl
265A	tBu	C(O)	CH2	CH2	CH2S(O)2Me
266A	tBu	CHOH	CH2	CH2	CH2S(O)2Me
267A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2Me
268A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2Me
269A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2Me
270A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2Me
271A	tBu	C(O)	CH2	CH2	CH2S(O)Me
272A	tBu	CHOH	CH2	CH2	CH2S(O2Me
273A	tBu	C(Me)OH	CH2	CH2	CH2S(O)Me
274A	tBu	C(O)	CH(Me)	CH2	CH2S(O)Me
275A	tBu	CHOH	CH(Me)	CH2	CH2S(O)Me
276A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)Me
277A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2Me
278A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2Me
279A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2Me
280A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2Me
281A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2Me
282A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2Me
283A	tBu	C(O)	CH2	CH2	CH2CH2S(O)Me
284A	tBu	CHOH	CH2	CH2	CH2CH2S(O)Me
285A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)Me
286A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)Me
287A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)Me
288A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)Me
289A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2Me
290A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2Me
291A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2Me
292A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2Me
293A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2Me
294A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2Me

295A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)Me
296A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)Me
297A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)Me
298A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)Me
299A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)Me
300A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)Me
301A	tBu	C(O)	CH2	CH2	CH2S(O)2Et
302A	tBu	CHOH	CH2	CH2	CH2S(O)2Et
303A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2Et
304A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2Et
305A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2Et
306A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2Et
307A	tBu	C(O)	CH2	CH2	CH2S(O)Et
308A	tBu	CHOH	CH2	CH2	CH2S(O)Et
309A	tBu	C(Me)OH	CH2	CH2	CH2S(O)Et
310A	tBu	C(O)	CH(Me)	CH2	CH2S(O)Et
311A	tBu	CHOH	CH(Me)	CH2	CH2S(O)Et
312A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)Et
313A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2Et
314A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2Et
315A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2Et
316A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2Et
317A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2Et
318A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2Et
319A	tBu	C(O)	CH2	CH2	CH2CH2S(O)Et
320A	tBu	CHOH	CH2	CH2	CH2CH2S(O)Et
321A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)Et
322A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)Et
323A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)Et
324A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)Et
325A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2Et

326A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2Et
327A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2Et
328A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2Et
329A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2Et
330A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2Et
331A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)Et
332A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)Et
333A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)Et
334A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)Et
335A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)Et
336A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)Et
337A	tBu	C(O)	CH2	CH2	CH2S(O)2iPr
338A	tBu	CHOH	CH2	CH2	CH2S(O)2iPr
339A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2iPr
340A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2iPr
341A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2iPr
342A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2iPr
343A	tBu	C(O)	CH2	CH2	CH2S(O)iPr
344A	tBu	CHOH	CH2	CH2	CH2S(O)iPr
345A	tBu	C(Me)OH	CH2	CH2	CH2S(O)iPr
346A	tBu	C(O)	CH(Me)	CH2	CH2S(O)iPr
347A	tBu	CHOH	CH(Me)	CH2	CH2S(O)iPr
348A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)iPr
349A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2iPr
350A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2iPr
351A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2iPr
352A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2iPr
353A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2iPr
354A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2iPr
355A	tBu	C(O)	CH2	CH2	CH2CH2S(O)iPr
356A	tBu	CHOH	CH2	CH2	CH2CH2S(O)iPr

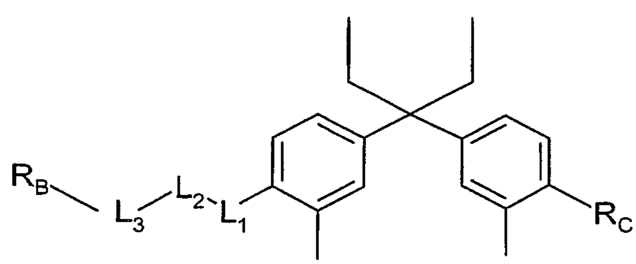
357A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)iPr
358A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)iPr
359A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)iPr
360A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)iPr
361A	tBu	C(O)	CH2	CH2	CH2S(O)2tBu
362A	tBu	CHOH	CH2	CH2	CH2S(O)2tBu
363A	tBu	C(Me)OH	CH2	CH2	CH2S(O)2tBu
364A	tBu	C(O)	CH(Me)	CH2	CH2S(O)2tBu
365A	tBu	CHOH	CH(Me)	CH2	CH2S(O)2tBu
366A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)2tBu
367A	tBu	C(O)	CH2	CH2	CH2S(O)tBu
368A	tBu	CHOH	CH2	CH2	CH2S(O)tBu
369A	tBu	C(Me)OH	CH2	CH2	CH2S(O)tBu
370A	tBu	C(O)	CH(Me)	CH2	CH2S(O)tBu
371A	tBu	CHOH	CH(Me)	CH2	CH2S(O)tBu
372A	tBu	C(Me)OH	CH(Me)	CH2	CH2S(O)tBu
373A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2tBu
374A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2tBu
375A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2tBu
376A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2tBu
377A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2tBu
378A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2tBu
379A	tBu	C(O)	CH2	CH2	CH2CH2S(O)tBu
380A	tBu	CHOH	CH2	CH2	CH2CH2S(O)tBu
381A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)tBu
382A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)tBu
383A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)tBu
384A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)tBu
385A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2NH2
386A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2NH2
387A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2NH2

388A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2NH2
389A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2NH2
390A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2NH2
391A	tBu	C(O)	CH2	CH2	CH2CH2S(O)NH2
392A	tBu	CHOH	CH2	CH2	CH2CH2S(O)NH2
393A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)NH2
394A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)NH2
395A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)NH2
396A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)NH2
397A	tBu	C(O)	CH2	CH2	CH2CH2S(O)2NMe2
398A	tBu	CHOH	CH2	CH2	CH2CH2S(O)2NMe2
399A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)2NMe2
400A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)2NMe2
401A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)2NMe2
402A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)2NMe2
403A	tBu	C(O)	CH2	CH2	CH2CH2S(O)NMe2
404A	tBu	CHOH	CH2	CH2	CH2CH2S(O)NMe2
405A	tBu	C(Me)OH	CH2	CH2	CH2CH2S(O)NMe2
406A	tBu	C(O)	CH(Me)	CH2	CH2CH2S(O)NMe2
407A	tBu	CHOH	CH(Me)	CH2	CH2CH2S(O)NMe2
408A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2S(O)NMe2
409A	tBu	C(O)	CH2	CH2	C(O)CH2S(O)2Me
410A	tBu	CHOH	CH2	CH2	C(O)CH2S(O)2Me
411A	tBu	C(Me)OH	CH2	CH2	C(O)CH2S(O)2Me
412A	tBu	C(O)	CH(Me)	CH2	C(O)CH2S(O)2Me
413A	tBu	CHOH	CH(Me)	CH2	C(O)CH2S(O)2Me
414A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2S(O)2Me
415A	tBu	C(O)	CH2	CH2	C(O)CH2S(O)Me
416A	tBu	CHOH	CH2	CH2	C(O)CH2S(O)Me
417A	tBu	C(Me)OH	CH2	CH2	C(O)CH2S(O)Me
418A	tBu	C(O)	CH(Me)	CH2	C(O)CH2S(O)Me

419A	tBu	CHOH	CH(Me)	CH2	C(O)CH2S(O)Me
420A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2S(O)Me
421A	tBu	C(O)	CH2	CH2	C(O)CH2CH2S(O)2Me
422A	tBu	CHOH	CH2	CH2	C(O)CH2CH2S(O)2Me
423A	tBu	C(Me)OH	CH2	CH2	C(O)CH2CH2S(O)2Me
424A	tBu	C(O)	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
425A	tBu	CHOH	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
426A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2CH2S(O)2Me
427A	tBu	C(O)	CH2	CH2	C(O)CH2CH2S(O)Me
428A	tBu	CHOH	CH2	CH2	C(O)CH2CH2S(O)Me
429A	tBu	C(Me)OH	CH2	CH2	C(O)CH2CH2S(O)Me
430A	tBu	C(O)	CH(Me)	CH2	C(O)CH2CH2S(O)Me
431A	tBu	CHOH	CH(Me)	CH2	C(O)CH2CH2S(O)Me
432A	tBu	C(Me)OH	CH(Me)	CH2	C(O)CH2CH2S(O)Me
433A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)2NH2
434A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)2NH2
435A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)2NH2
436A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
437A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
438A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)2NH2
439A	tBu	C(O)	CH2	CH2	CH2CH2CH2S(O)NH2
440A	tBu	CHOH	CH2	CH2	CH2CH2CH2S(O)NH2
441A	tBu	C(Me)OH	CH2	CH2	CH2CH2CH2S(O)NH2
442A	tBu	C(O)	CH(Me)	CH2	CH2CH2CH2S(O)NH2
443A	tBu	CHOH	CH(Me)	CH2	CH2CH2CH2S(O)NH2
444A	tBu	C(Me)OH	CH(Me)	CH2	CH2CH2CH2S(O)NH2
445A	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
446A	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
447A	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-one-5-yl
448A	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
449A	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl

450A	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-one-5-yl
451A	tBu	C(O)	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
452A	tBu	CHOH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
453A	tBu	C(Me)OH	CH2	CH2	1,3,4-oxadiazolin-2-thione-5-yl
454A	tBu	C(O)	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
455A	tBu	CHOH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
456A	tBu	C(Me)OH	CH(Me)	CH2	1,3,4-oxadiazolin-2-thione-5-yl
457A	tBu	C(O)	CH2	CH2	imidazolidine-2,4-dione-5-yl
458A	tBu	CHOH	CH2	CH2	imidazolidine-2,4-dione-5-yl
459A	tBu	C(Me)OH	CH2	CH2	imidazolidine-2,4-dione-5-yl
460A	tBu	C(O)	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
461A	tBu	CHOH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
462A	tBu	C(Me)OH	CH(Me)	CH2	imidazolidine-2,4-dione-5-yl
463A	tBu	C(O)	CH2	CH2	isoxazol-3-ol-5-yl
464A	tBu	CHOH	CH2	CH2	isoxazol-3-ol-5-yl
465A	tBu	C(Me)OH	CH2	CH2	isoxazol-3-ol-5-yl
466A	tBu	C(O)	CH(Me)	CH2	isoxazol-3-ol-5-yl
467A	tBu	CHOH	CH(Me)	CH2	isoxazol-3-ol-5-yl
468A	tBu	C(Me)OH	CH(Me)	CH2	isoxazol-3-ol-5-yl

6. A compound or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1B thru 162B, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the row following the compound code number, as set out in the following Table 3 :

Table 3

	R_B	L_3	L_2	L_1	R_C
1B	tBu	C(O)	CH2	O	-C(O)NH-CH_2-C(O)OH
2B	tBu	CHOH	CH2	O	-C(O)NH-CH_2-C(O)OH
3B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH_2-C(O)OH
4B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
5B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
6B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH_2-C(O)OH
7B	tBu	C(O)	CH2	O	-C(O)NH-CH(Me)-C(O)OH
8B	tBu	CHOH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
9B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
10B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
11B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
12B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
13B	tBu	C(O)	CH2	O	-C(O)NH-CH(Et)-C(O)OH
14B	tBu	CHOH	CH2	O	-C(O)NH-CH(Et)-C(O)OH
15B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Et)-C(O)OH
16B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
17B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
18B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Et)-C(O)OH
19B	tBu	C(O)	CH2	O	-C(O)NH-$C(Me)_2$-C(O)OH
20B	tBu	CHOH	CH2	O	-C(O)NH-$C(Me)_2$-C(O)OH
21B	tBu	C(Me)OH	CH2	O	-C(O)NH-$C(Me)_2$-C(O)OH
22B	tBu	C(O)	CH(Me)	O	-C(O)NH-$C(Me)_2$-C(O)OH
23B	tBu	CHOH	CH(Me)	O	-C(O)NH-$C(Me)_2$-C(O)OH
24B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-$C(Me)_2$-C(O)OH
25B	tBu	C(O)	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
26B	tBu	CHOH	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
27B	tBu	C(Me)OH	CH2	O	-C(O)NH-CMe(Et)-C(O)OH
28B	tBu	C(O)	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH
29B	tBu	CHOH	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH

30B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CMe(Et)-C(O)OH
31B	tBu	C(O)	CH2	O	-C(O)NH-CH(F)-C(O)OH
32B	tBu	CHOH	CH2	O	-C(O)NH-CH(F)-C(O)OH
33B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(F)-C(O)OH
34B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
35B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
36B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(F)-C(O)OH
37B	tBu	C(O)	CH2	O	-C(O)NH-CH(CF_3)-C(O)OH
38B	tBu	CHOH	CH2	O	-C(O)NH-CH(CF_3)-C(O)OH
39B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(CF_3)-C(O)OH
40B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
41B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
42B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(CF_3)-C(O)OH
43B	tBu	C(O)	CH2	O	-C(O)NH-CH(OH)-C(O)OH
44B	tBu	CHOH	CH2	O	-C(O)NH-CH(OH)-C(O)OH
45B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(OH)-C(O)OH
46B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
47B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
48B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(OH)-C(O)OH
49B	tBu	C(O)	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
50B	tBu	CHOH	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
51B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
52B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
53B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
54B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(cyclopropyl)-C(O)OH
55B	tBu	C(O)	CH2	O	-C(O)NH-CH(Me)-C(O)OH
56B	tBu	CHOH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
57B	tBu	C(Me)OH	CH2	O	-C(O)NH-CH(Me)-C(O)OH
58B	tBu	C(O)	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
59B	tBu	CHOH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH
60B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CH(Me)-C(O)OH

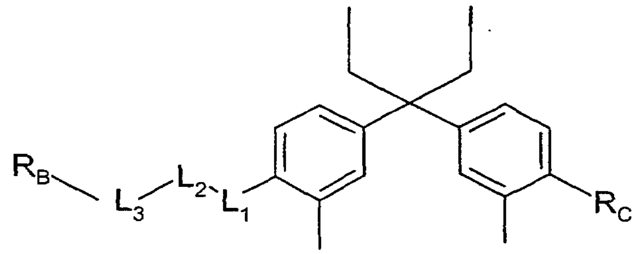
61B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
62B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
63B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)$_2$-C(O)OH
64B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
65B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
66B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)$_2$-C(O)OH
67B	tBu	C(O)	CH2	O	-C(O)NH-CF(Me)-C(O)OH
68B	tBu	CHOH	CH2	O	-C(O)NH-CF(Me)-C(O)OH
69B	tBu	C(Me)OH	CH2	O	-C(O)NH-CF(Me)-C(O)OH
70B	tBu	C(O)	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH
71B	tBu	CHOH	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH
72B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-CF(Me)-C(O)OH
73B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
74B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
75B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
76B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
77B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
78B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
79B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
80B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
81B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(OH)-C(O)OH
82B	tBu	C(O)	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
83B	tBu	CHOH	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
84B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-C(Me)(OH)-C(O)OH
85B	tBu	C(O)	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H
86B	tBu	CHOH	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H
87B	tBu	C(Me)OH	CH2	O	-C(O)NH-C(Me)(cyclopropyl)CO$_2$H
88B	tBu	C(O)	CH(Me)	O	-C(O)NH-

					$C(Me)(cyclopropyl)CO_2H$
89B	tBu	CHOH	CH(Me)	O	-C(O)NH-$C(Me)(cyclopropyl)CO_2H$
90B	tBu	C(Me)OH	CH(Me)	O	-C(O)NH-$C(Me)(cyclopropyl)CO_2H$
91B	tBu	C(O)	CH2	O	-C(O)NMe-CH_2-C(O)OH
92B	tBu	CHOH	CH2	O	-C(O)NMe-CH_2-C(O)OH
93B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH_2-C(O)OH
94B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH
95B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH
96B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH_2-C(O)OH
97B	tBu	C(O)	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
98B	tBu	CHOH	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
99B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(Me)-C(O)OH
100B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
101B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
102B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(Me)-C(O)OH
103B	tBu	C(O)	CH2	O	-C(O)NMe-CH(F)-C(O)OH
104B	tBu	CHOH	CH2	O	-C(O)NMe-CH(F)-C(O)OH
105B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(F)-C(O)OH
106B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
107B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
108B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(F)-C(O)OH
109B	tBu	C(O)	CH2	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
110B	tBu	CHOH	CH2	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
111B	tBu	C(Me)OH	CH2	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
112B	tBu	C(O)	CH(Me)	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
113B	tBu	CHOH	CH(Me)	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
114B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-$CH(CF_3)$-C(O)OH
115B	tBu	C(O)	CH2	O	-C(O)NMe-CH(OH)-C(O)OH
116B	tBu	CHOH	CH2	O	-C(O)NMe-CH(OH)-C(O)OH

117B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(OH)-C(O)OH
118B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
119B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
120B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(OH)-C(O)OH
121B	tBu	C(O)	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
122B	tBu	CHOH	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
123B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
124B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
125B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
126B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CH(cyclopropyl)-C(O)OH
127B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
128B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
129B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)$_2$-C(O)OH
130B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
131B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
132B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)$_2$-C(O)OH
133B	tBu	C(O)	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
134B	tBu	CHOH	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
135B	tBu	C(Me)OH	CH2	O	-C(O)NMe-CF(Me)-C(O)OH
136B	tBu	C(O)	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
137B	tBu	CHOH	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
138B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-CF(Me)-C(O)OH
139B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
140B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH
141B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(CF$_3$)-C(O)OH

142B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(CF_3)-C(O)OH
143B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(CF_3)-C(O)OH
144B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(CF_3)-C(O)OH
145B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
146B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
147B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(OH)-C(O)OH
148B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
149B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
150B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(OH)-C(O)OH
151B	tBu	C(O)	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
152B	tBu	CHOH	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
153B	tBu	C(Me)OH	CH2	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
154B	tBu	C(O)	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
155B	tBu	CHOH	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
156B	tBu	C(Me)OH	CH(Me)	O	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
157B	tBu	C(O)	CH2	O	-C(O)-N(Me)-5-tetrazolyl
158B	tBu	CHOH	CH2	O	-C(O)-N(Me)-5-tetrazolyl
159B	tBu	C(Me)OH	CH2	O	-C(O)-N(Me)-5-tetrazolyl
160B	tBu	C(O)	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl
161B	tBu	CHOH	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl
162B	tBu	C(Me)OH	CH(Me)	O	-C(O)-N(Me)-5-tetrazolyl

7. A compound or a pharmaceutically acceptable salt or an ester prodrug derivative thereof represented by the formula:



where said compound is selected from a compound code numbered 1C thru 162C, with each compound having the specific selection of substituents R_B, R_C, L_1, L_2, and L_3 shown in the row following the compound code number, as set out in the following Table 4 :

Table 4

	R_B	L_3	L_2	L_1	R_C
1C	tBu	C(O)	CH2	CH2	-C(O)NH-CH$_2$-C(O)OH
2C	tBu	CHOH	CH2	CH2	-C(O)NH-CH$_2$-C(O)OH
3C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH$_2$-C(O)OH
4C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH$_2$-C(O)OH
5C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH$_2$-C(O)OH
6C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH$_2$-C(O)OH
7C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
8C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
9C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
10C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
11C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
12C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
13C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
14C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
15C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Et)-C(O)OH
16C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
17C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
18C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Et)-C(O)OH
19C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
20C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH

21C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
22C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
23C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
24C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
25C	tBu	C(O)	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
26C	tBu	CHOH	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
27C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CMe(Et)-C(O)OH
28C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH
29C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH
30C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CMe(Et)-C(O)OH
31C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
32C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
33C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(F)-C(O)OH
34C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
35C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
36C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(F)-C(O)OH
37C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
38C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
39C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
40C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
41C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
42C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(CF$_3$)-C(O)OH
43C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
44C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
45C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(OH)-C(O)OH
46C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
47C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
48C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(OH)-C(O)OH
49C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
50C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
51C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH

52C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
53C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
54C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(cyclopropyl)-C(O)OH
55C	tBu	C(O)	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
56C	tBu	CHOH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
57C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CH(Me)-C(O)OH
58C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
59C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
60C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CH(Me)-C(O)OH
61C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
62C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
63C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
64C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
65C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
66C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)$_2$-C(O)OH
67C	tBu	C(O)	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
68C	tBu	CHOH	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
69C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-CF(Me)-C(O)OH
70C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
71C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
72C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-CF(Me)-C(O)OH
73C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
74C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
75C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
76C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
77C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
78C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(CF$_3$)-C(O)OH
79C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
80C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
81C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
82C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH

83C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
84C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(OH)-C(O)OH
85C	tBu	C(O)	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
86C	tBu	CHOH	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
87C	tBu	C(Me)OH	CH2	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
88C	tBu	C(O)	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
89C	tBu	CHOH	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
90C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NH-C(Me)(cyclopropyl)CO_2H
91C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
92C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
93C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH_2-C(O)OH
94C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
95C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
96C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH_2-C(O)OH
97C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
98C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
99C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(Me)-C(O)OH
100C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
101C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
102C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(Me)-C(O)OH
103C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
104C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
105C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(F)-C(O)OH
106C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH
107C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH

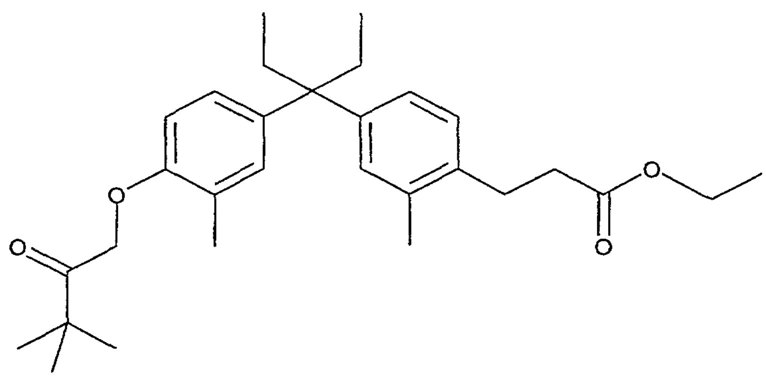
108C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(F)-C(O)OH
109C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
110C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
111C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
112C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
113C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
114C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(CF_3)-C(O)OH
115C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH
116C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH
117C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(OH)-C(O)OH
118C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
119C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
120C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(OH)-C(O)OH
121C	tBu	C(O)	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
122C	tBu	CHOH	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
123C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
124C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
125C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
126C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CH(cyclopropyl)-C(O)OH
127C	tBu	C(O)	CH2	CH2	-C(O)NMe-C($Me)_2$-C(O)OH
128C	tBu	CHOH	CH2	CH2	-C(O)NMe-C($Me)_2$-C(O)OH
129C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C($Me)_2$-C(O)OH
130C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C($Me)_2$-C(O)OH
131C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C($Me)_2$-C(O)OH
132C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C($Me)_2$-C(O)OH

133C	tBu	C(O)	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
134C	tBu	CHOH	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
135C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-CF(Me)-C(O)OH
136C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
137C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
138C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-CF(Me)-C(O)OH
139C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
140C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
141C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
142C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
143C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
144C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(CF_3)-C(O)OH
145C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
146C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
147C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
148C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
149C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
150C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(OH)-C(O)OH
151C	tBu	C(O)	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
152C	tBu	CHOH	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
153C	tBu	C(Me)OH	CH2	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
154C	tBu	C(O)	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
155C	tBu	CHOH	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
156C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)NMe-C(Me)(cyclopropyl)-C(O)OH
157C	tBu	C(O)	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl

158C	tBu	CHOH	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl
159C	tBu	C(Me)OH	CH2	CH2	-C(O)-N(Me)-5-tetrazolyl
160C	tBu	C(O)	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl
161C	tBu	CHOH	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl
162C	tBu	C(Me)OH	CH(Me)	CH2	-C(O)-N(Me)-5-tetrazolyl

8. A compound or a pharmaceutically acceptable salt or a prodrug derivative thereof selected from compounds AA thru CY:

AA)



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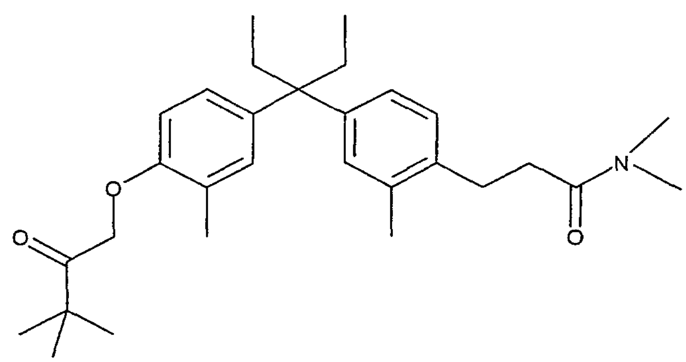
AE)



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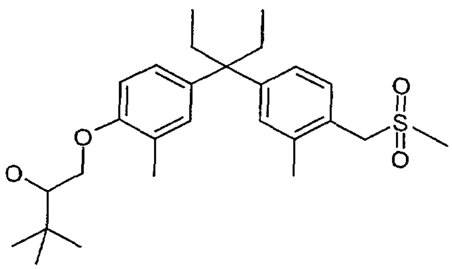
AP)



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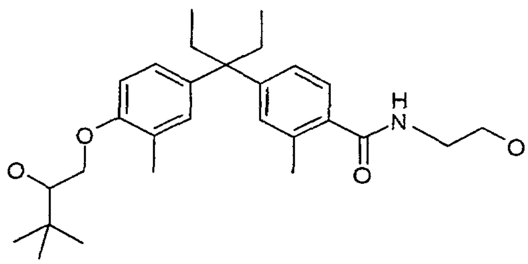
AR)



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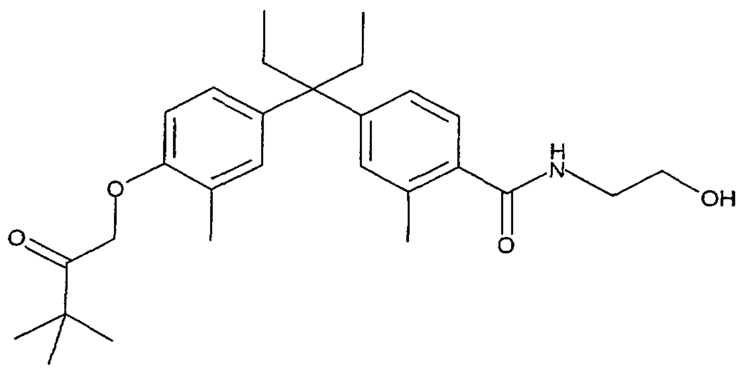
AT)



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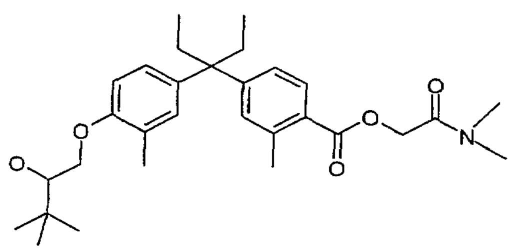
AW)



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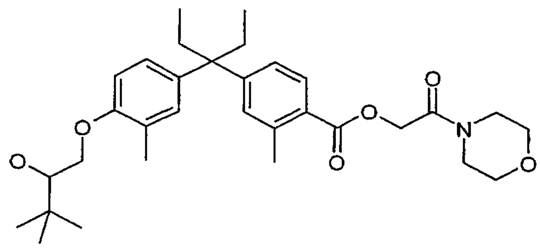
BA)



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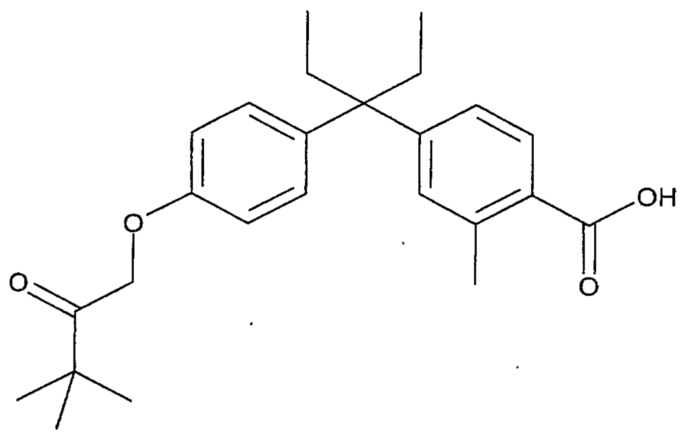
BE)



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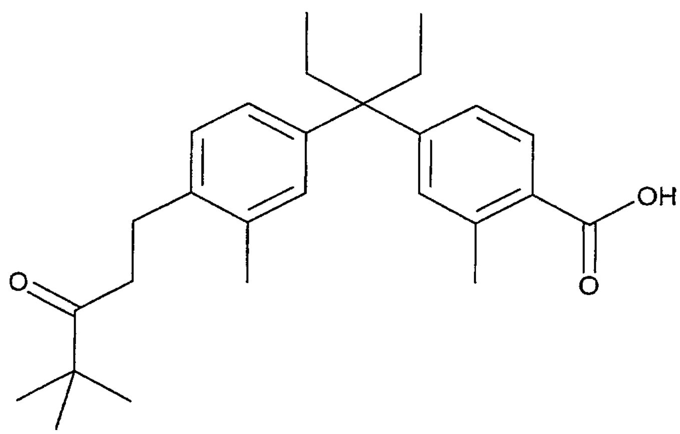
BH)



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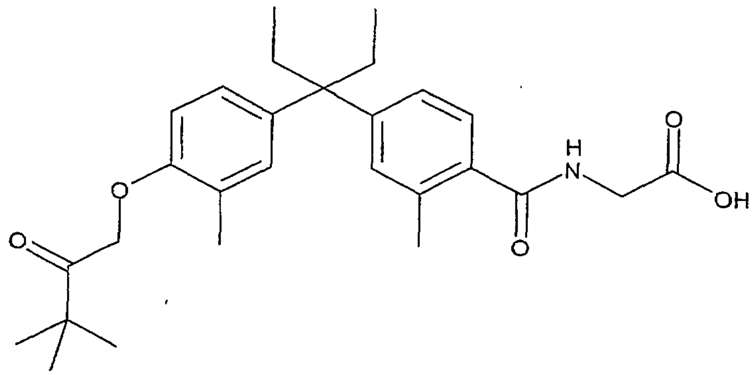
BI)



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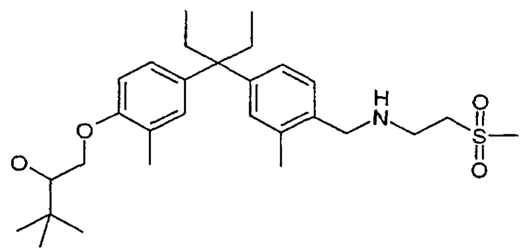
BJ)



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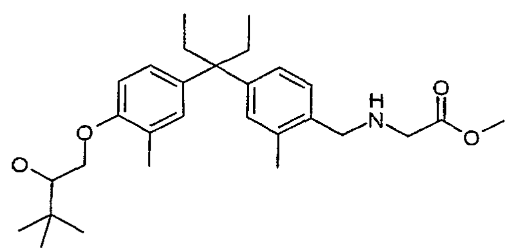
BN)



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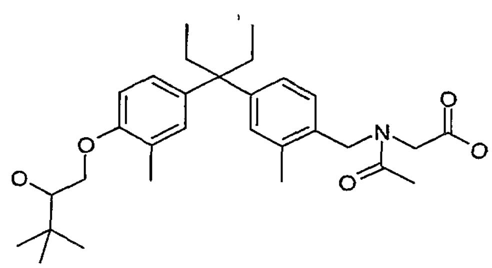
BP)



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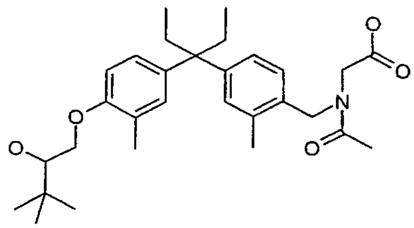
CA)



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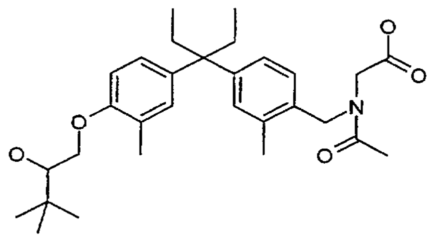
CB)



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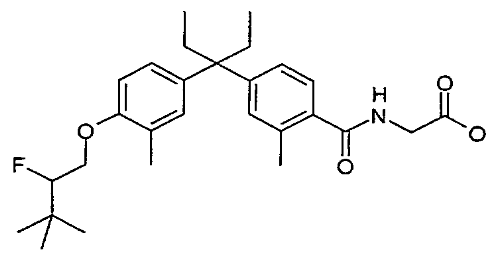
CC)



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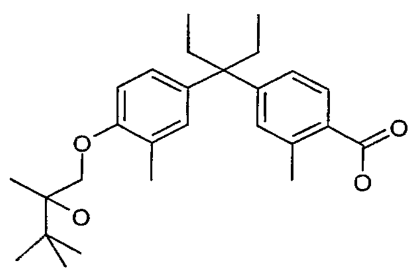
CE)



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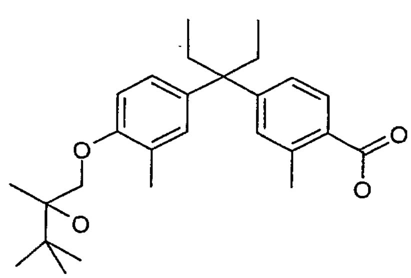
CF)



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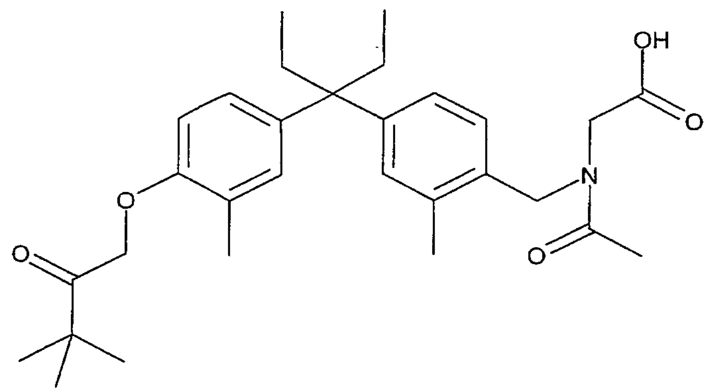
CI)



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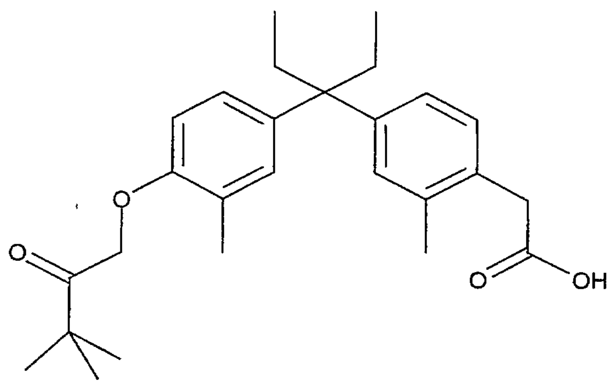
CL)



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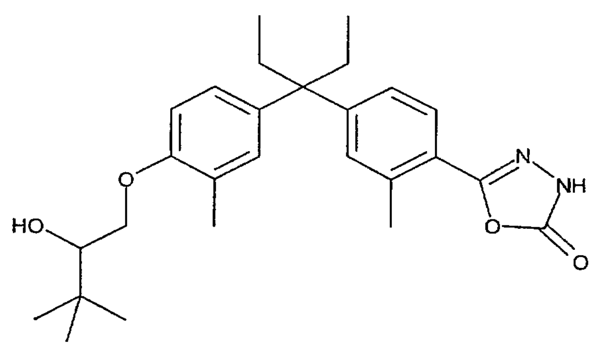
CM)



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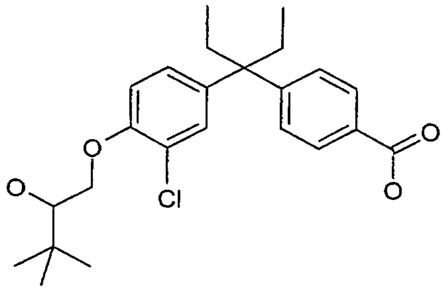
CN)



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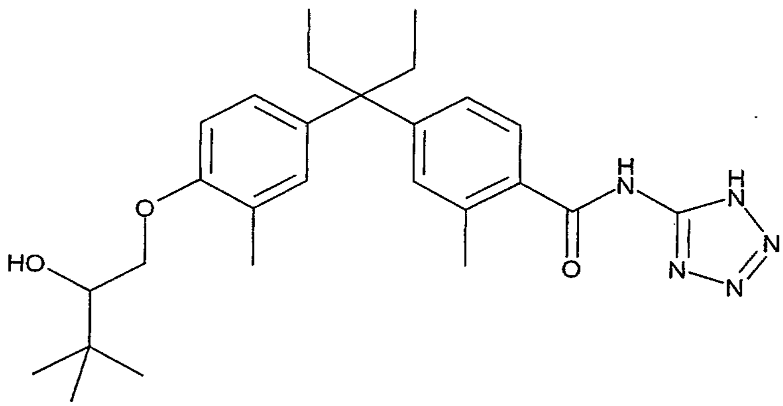
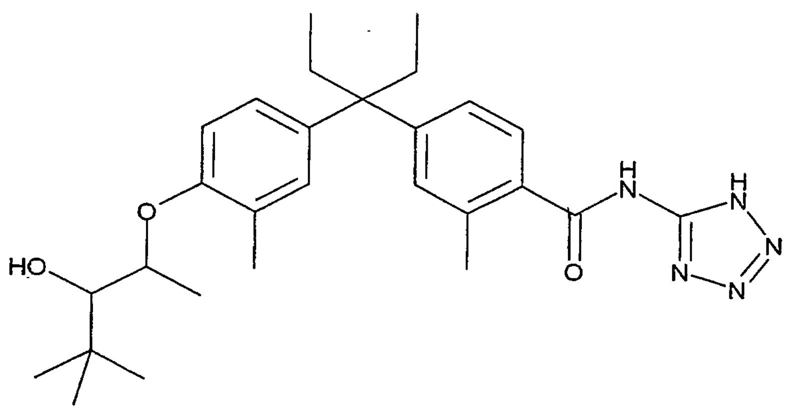
CP)



, or

CQ)



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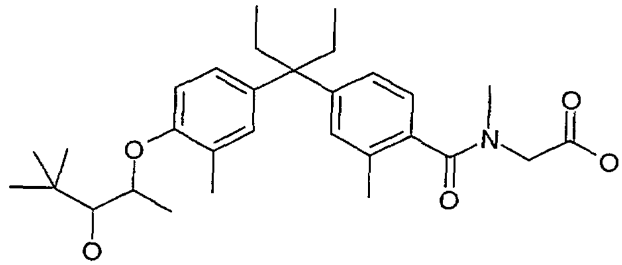
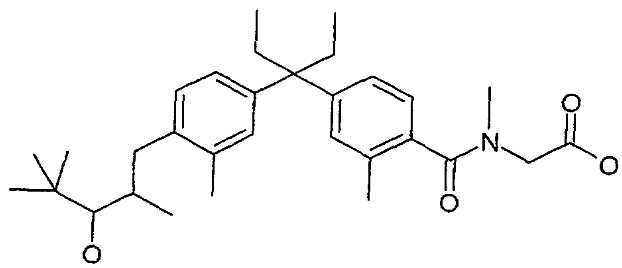
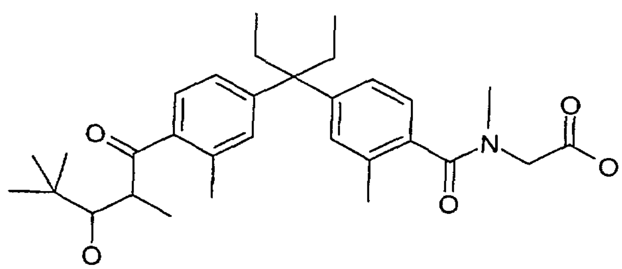
CR)



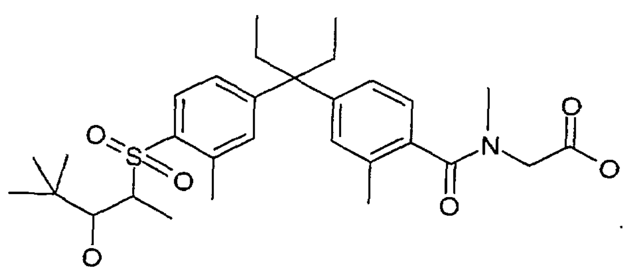
CS)



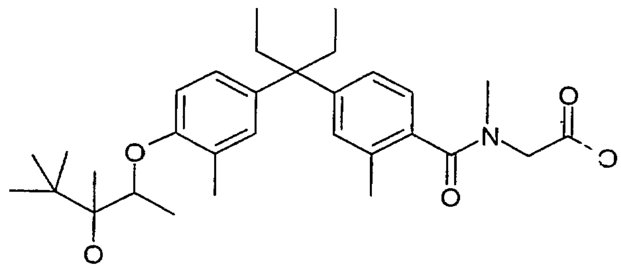
CT)



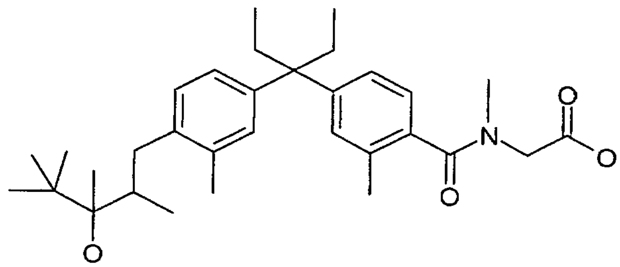
CU)



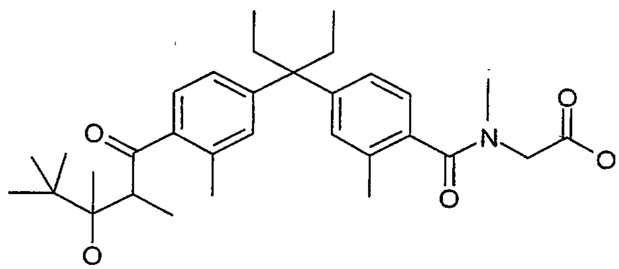
CV)



CW)

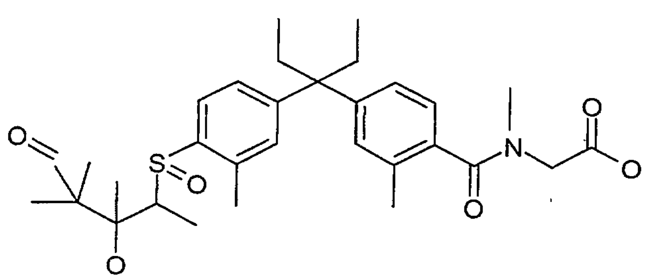


CX)



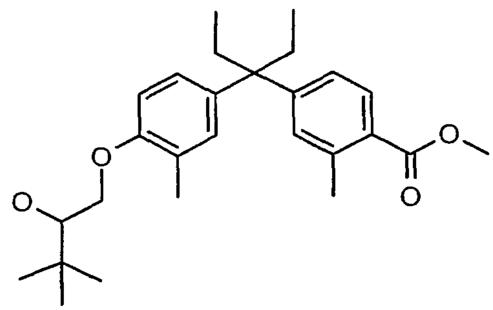
or

CY)

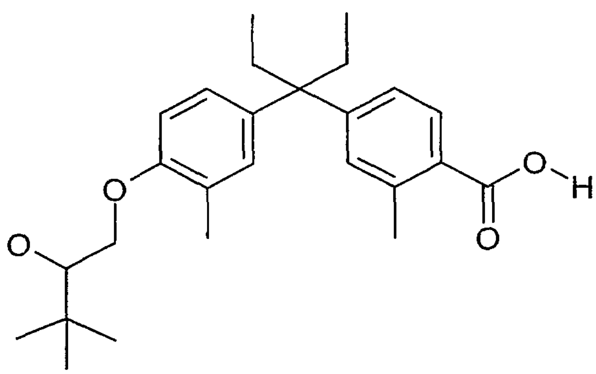


8. A compound or a pharmaceutically acceptable salt or prodrug derivative thereof selected from C-1 to C-55:

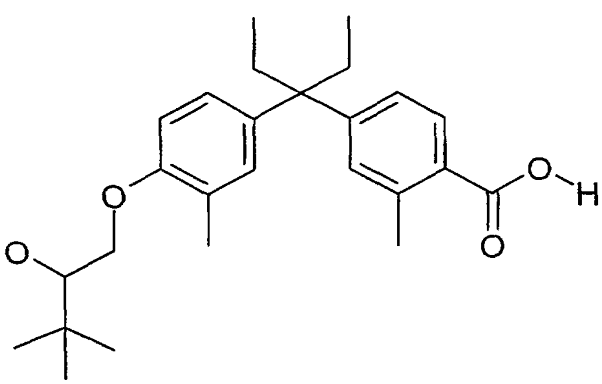
C-1)



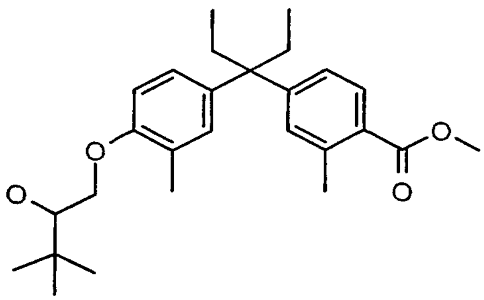
C-2)



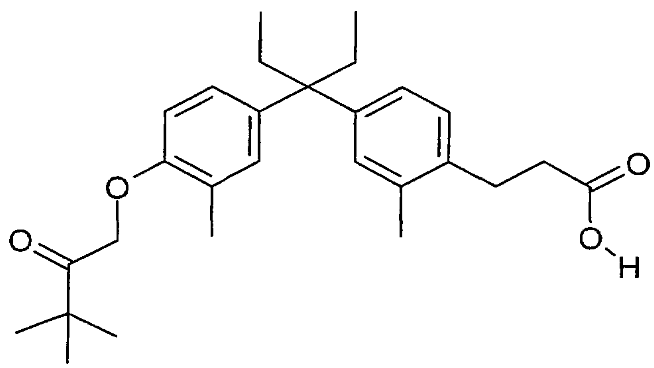
C-3)



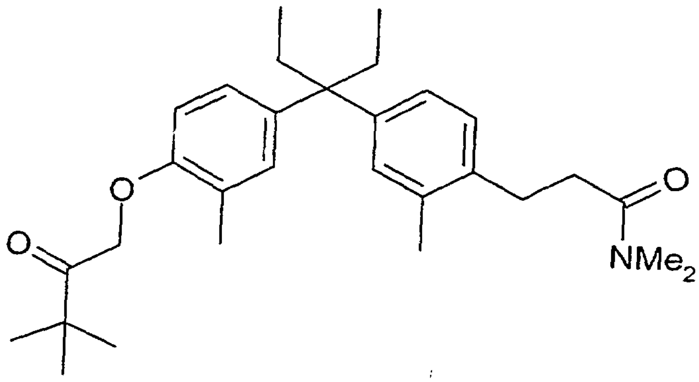
C-4)



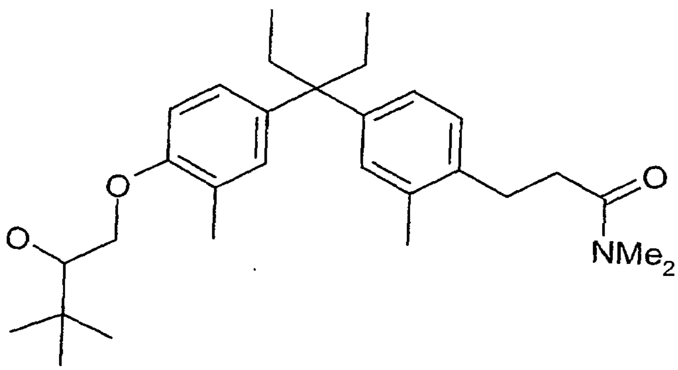
C-6)



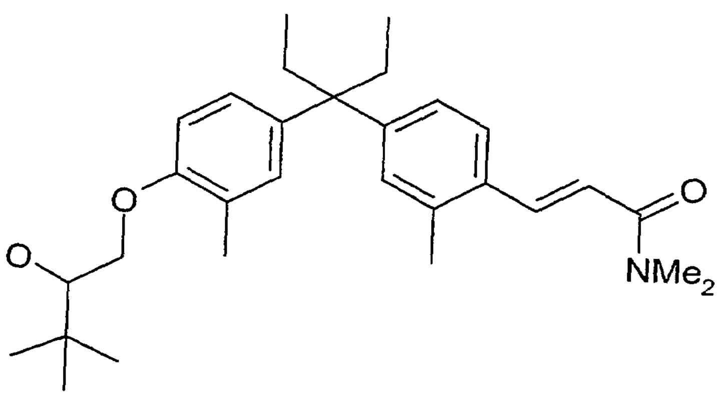
C-7)



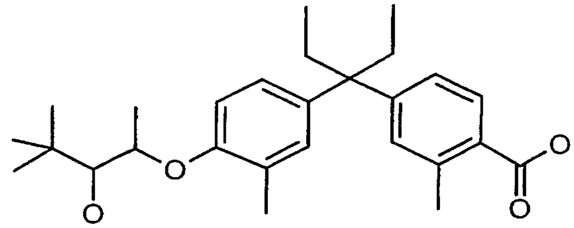
C-8)



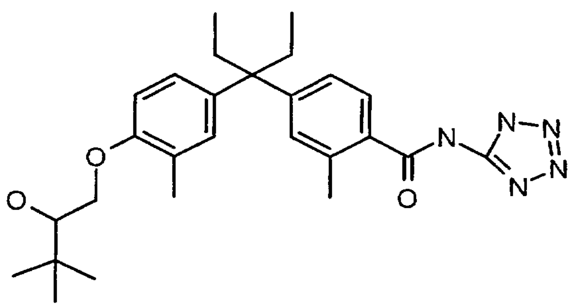
C-9)



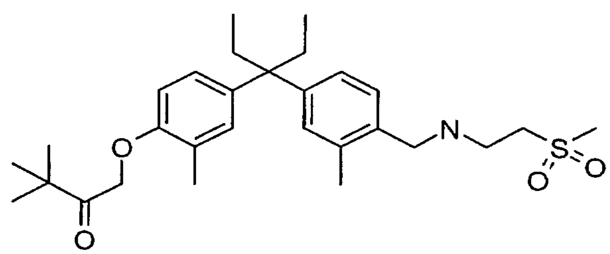
C-10)



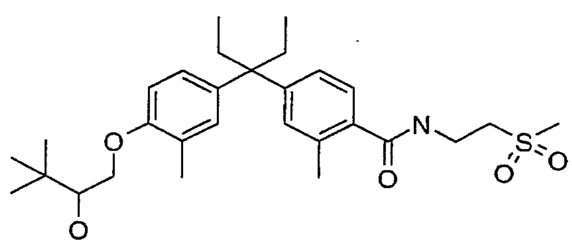
C-12)



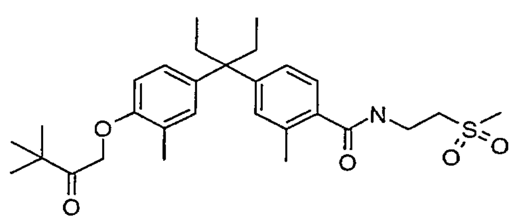
C-13)



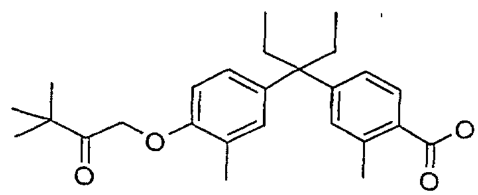
C-15)



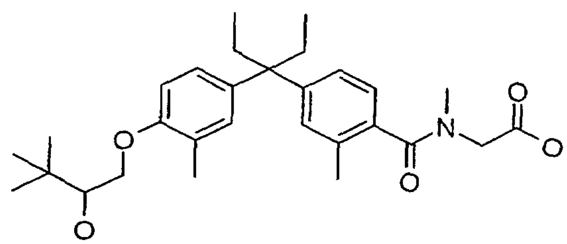
C-16)



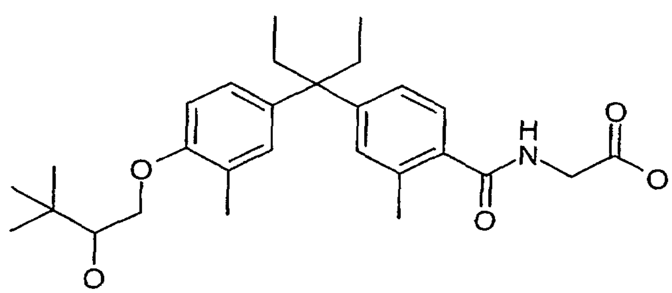
C-17)



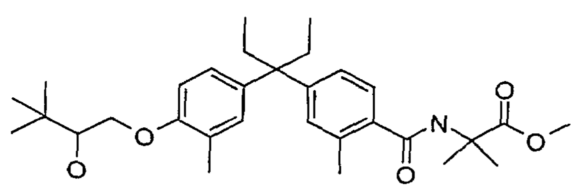
C-18)



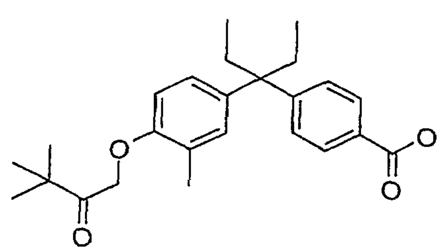
C-19)



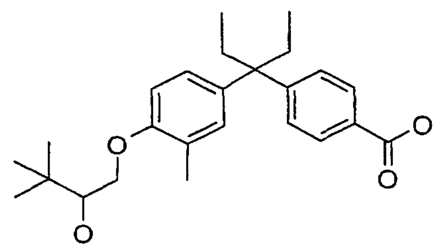
C-20)



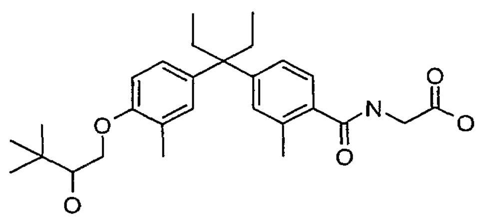
C-21)



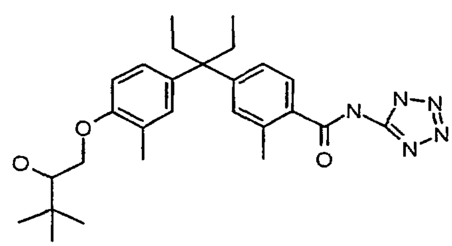
C-22)



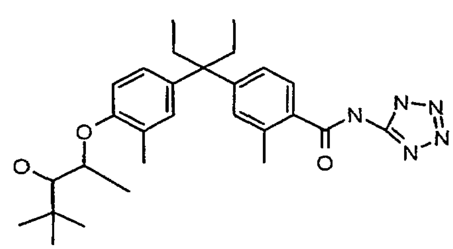
C-25)



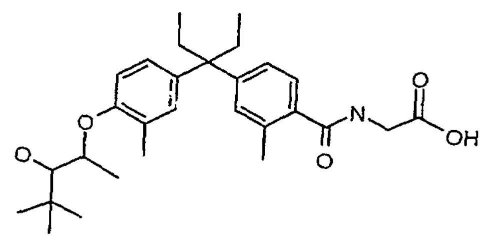
C-26)



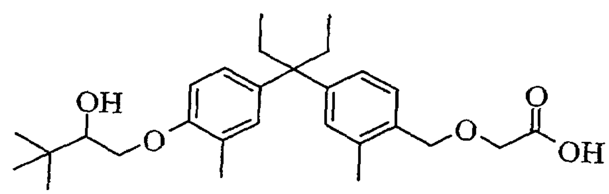
C-29)



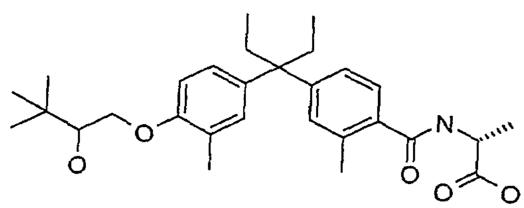
C-31)



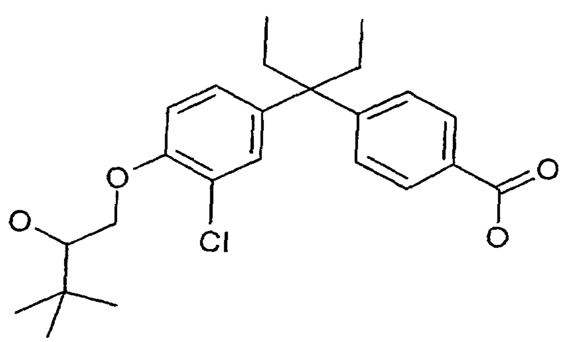
C-35)



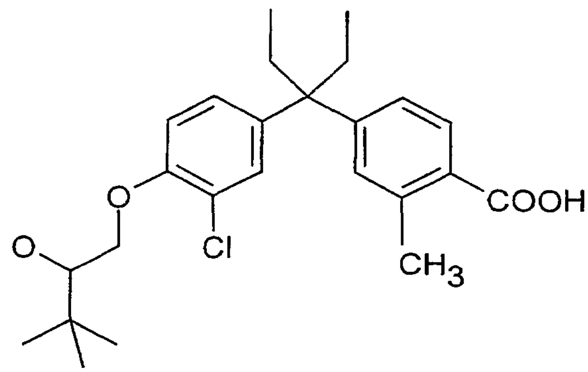
C-36)



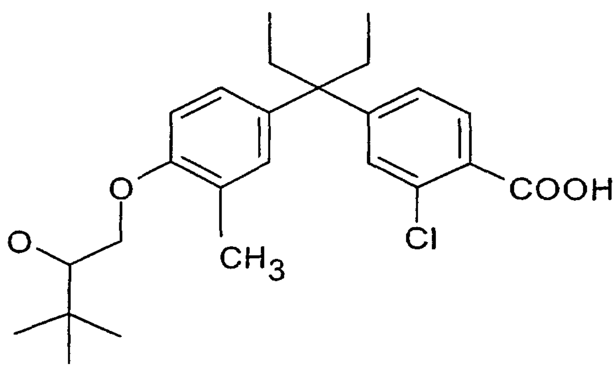
C-39)



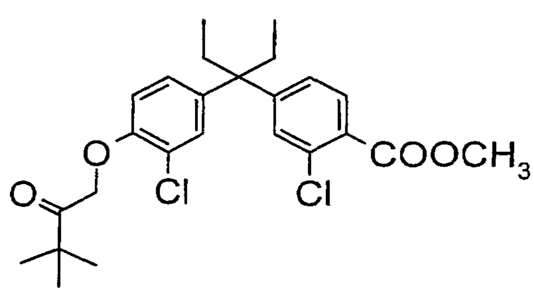
C-42)



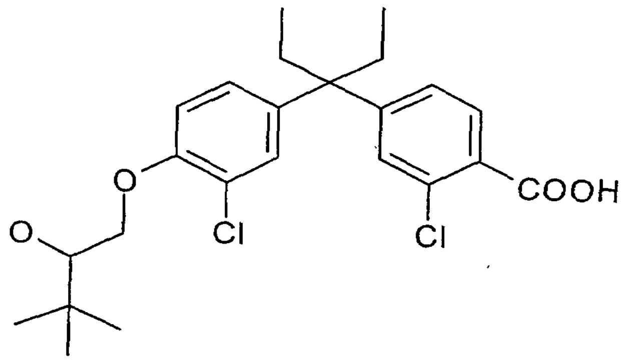
C-43)



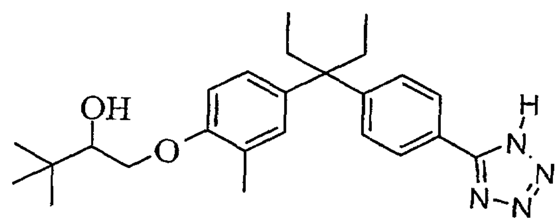
C-44)



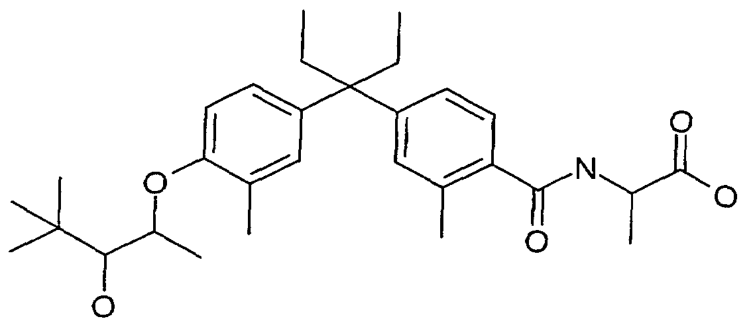
C-45)



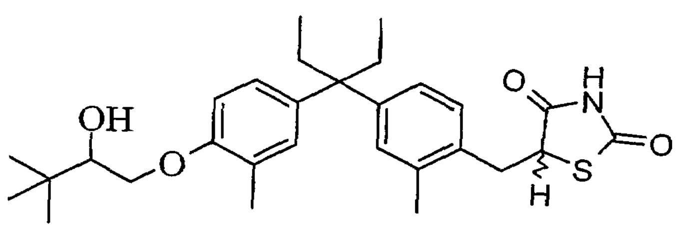
C-48)



C-52)

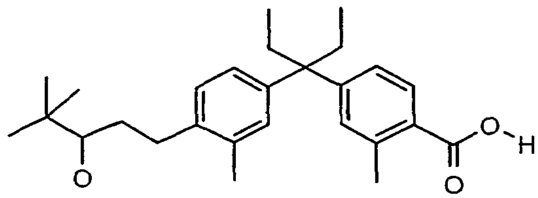


C-54)



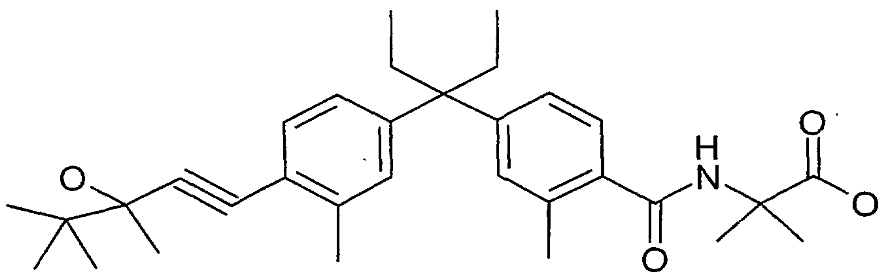
or

C-55)



9. A compound or a pharmaceutically acceptable salt oran ester prodrug derivative thereof selected from (TBU-1) to (TBU-86), as follows:

TBU-1)



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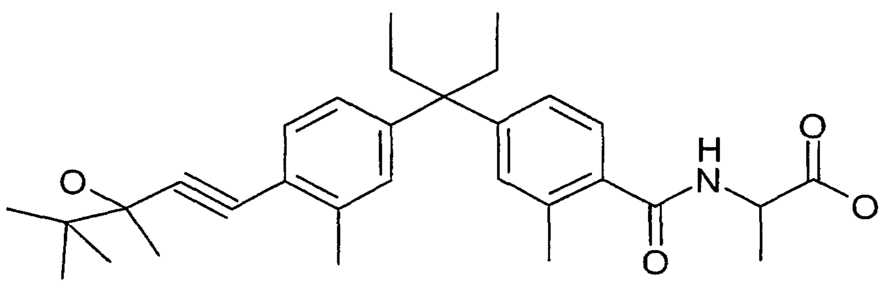
TBU-2)



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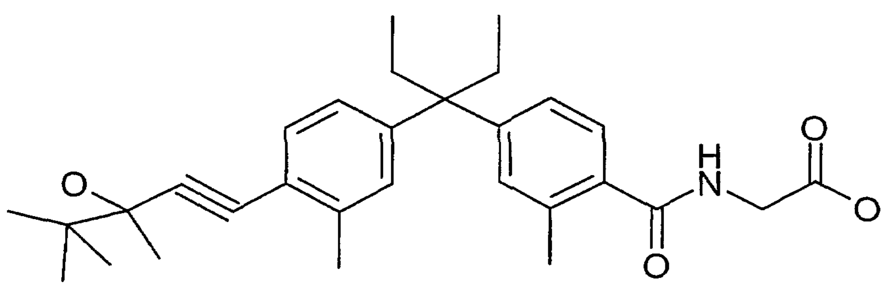
TBU-3)



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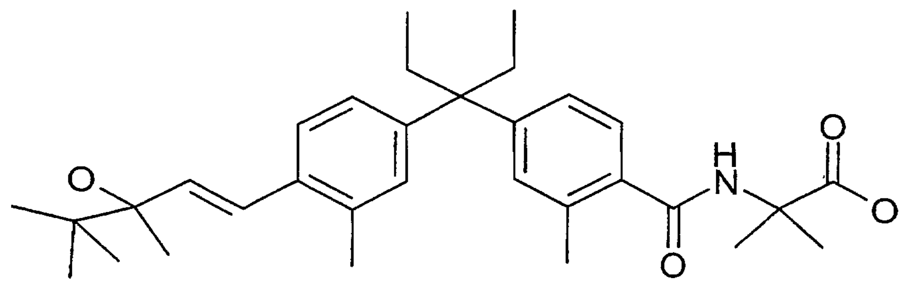
TBU-4)



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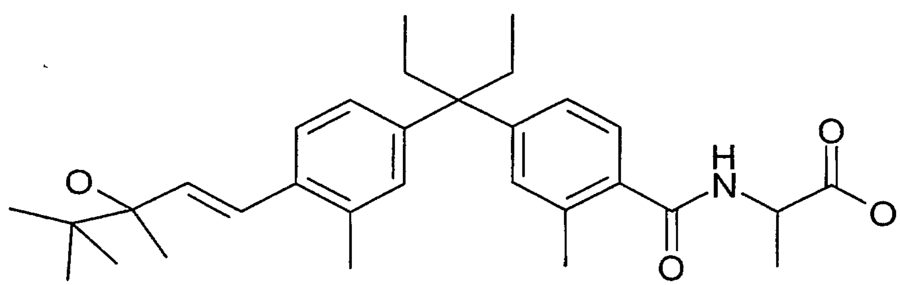
TBU-5)



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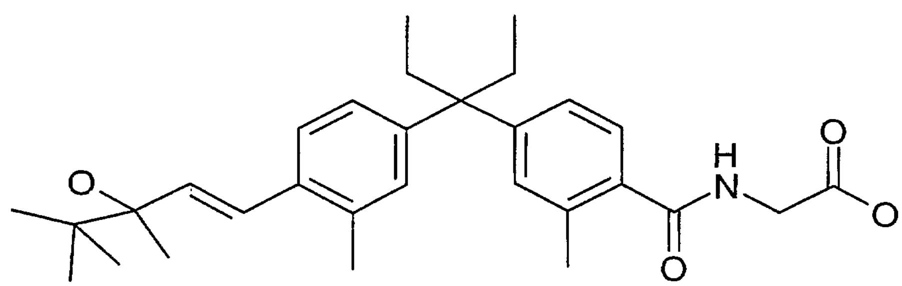
TBU-6)



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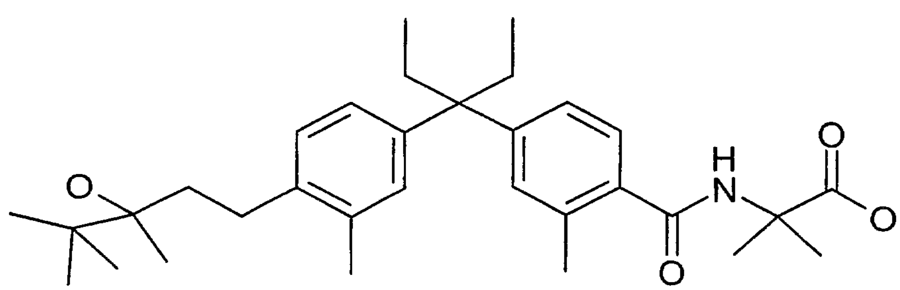
TBU-7)



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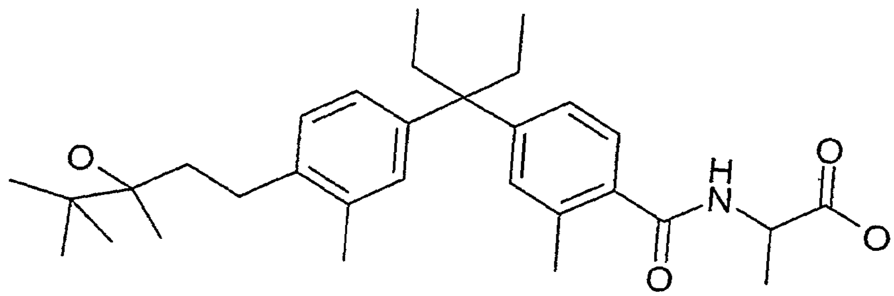
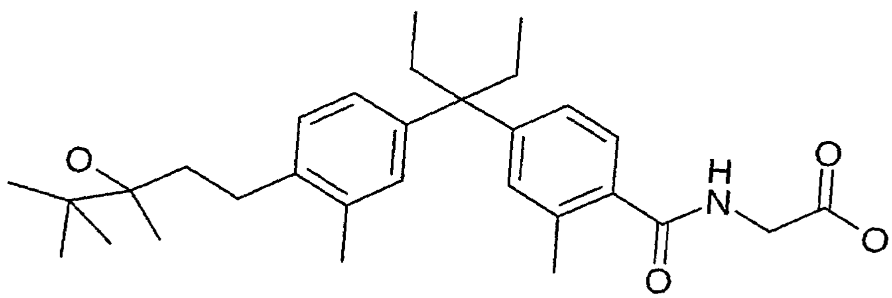
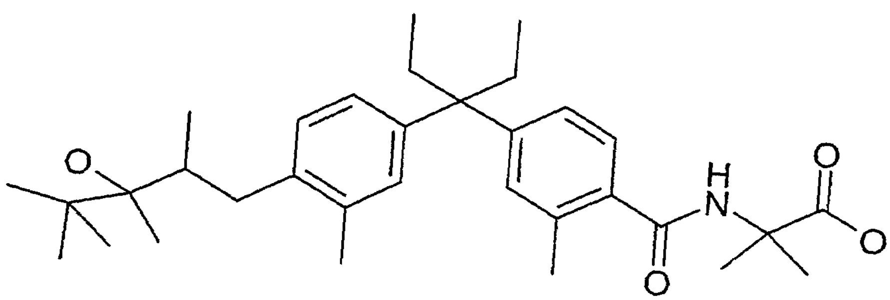
TBU-8)



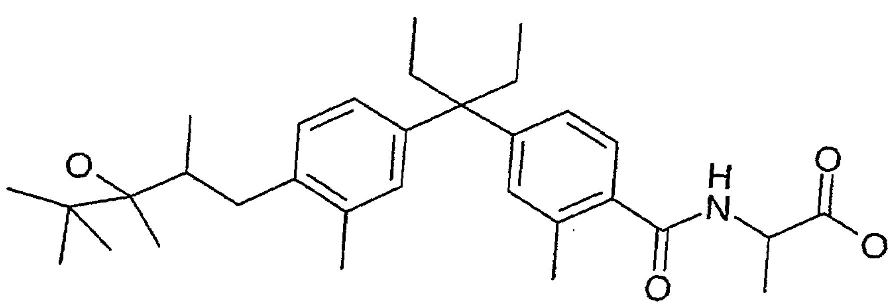
TBU-9) ,



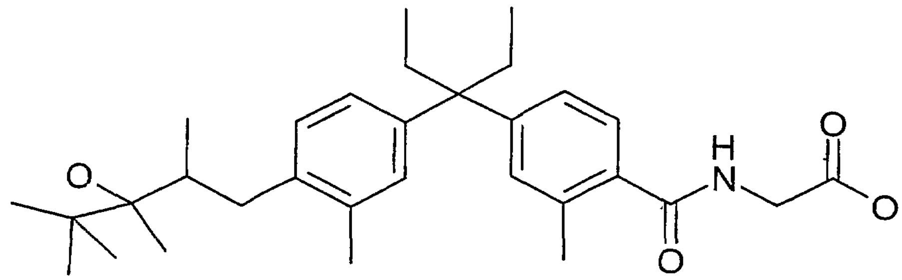
TBU-10) ,



TBU-11) ,



TBU-12) ,



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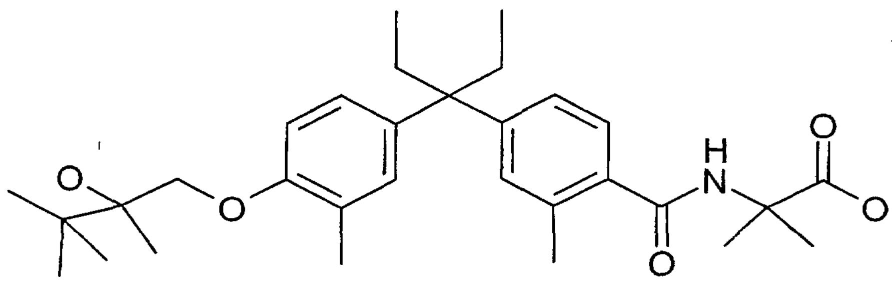
TBU-13)



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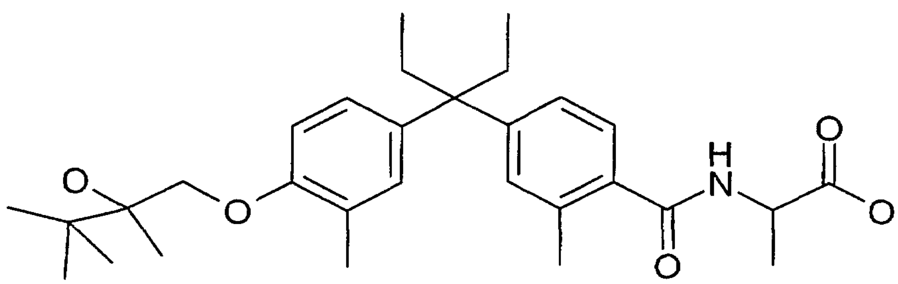
TBU-14)



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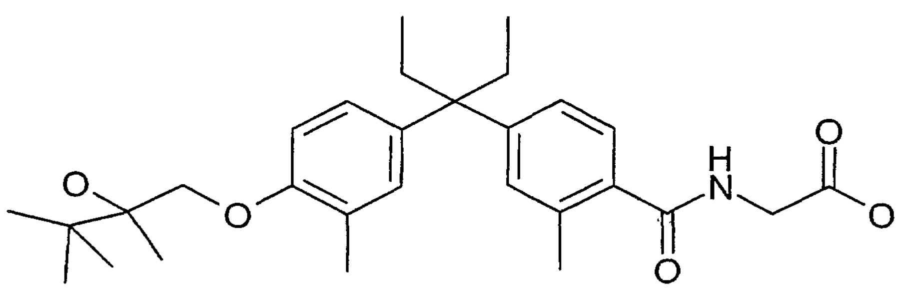

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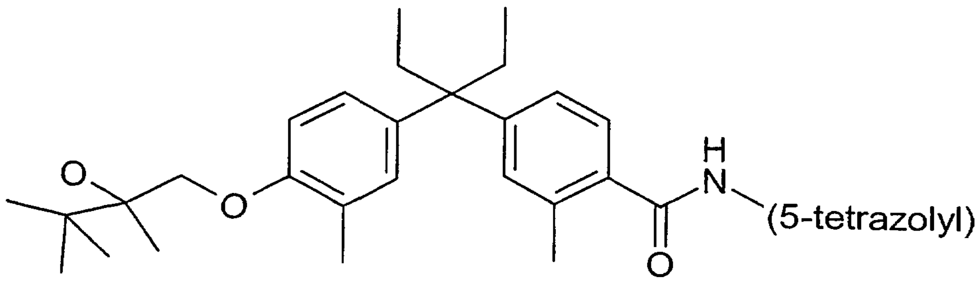

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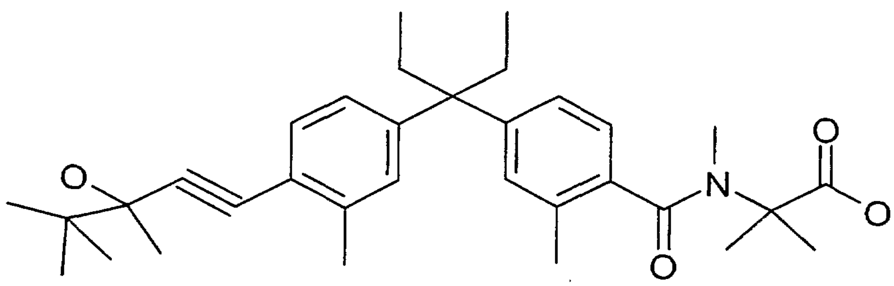

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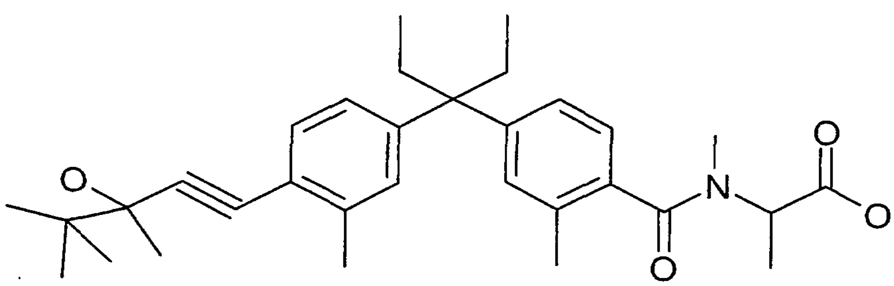

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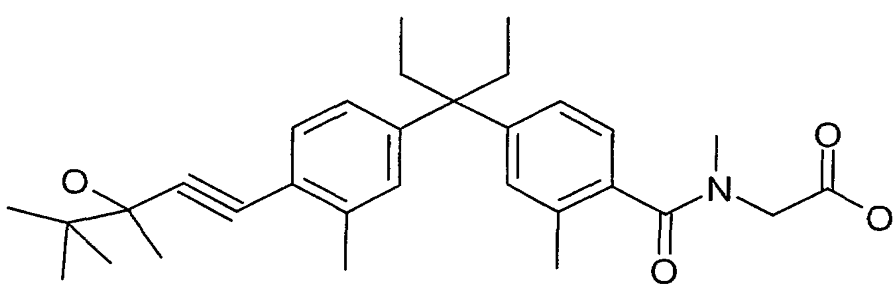

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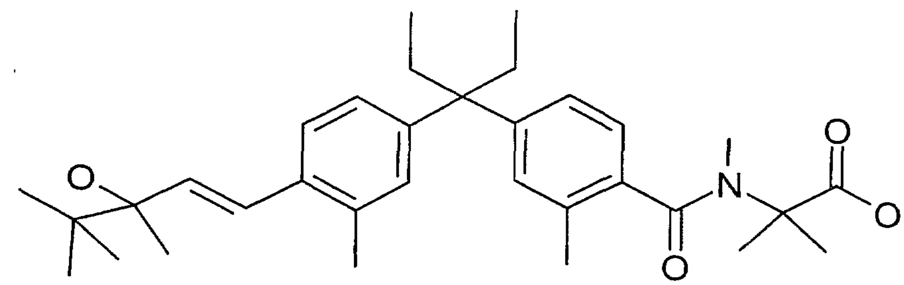

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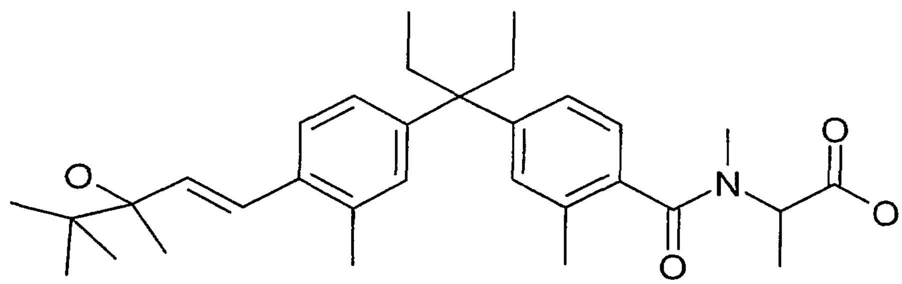

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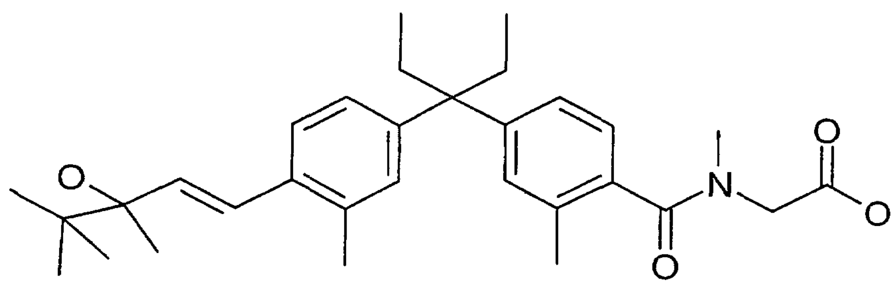

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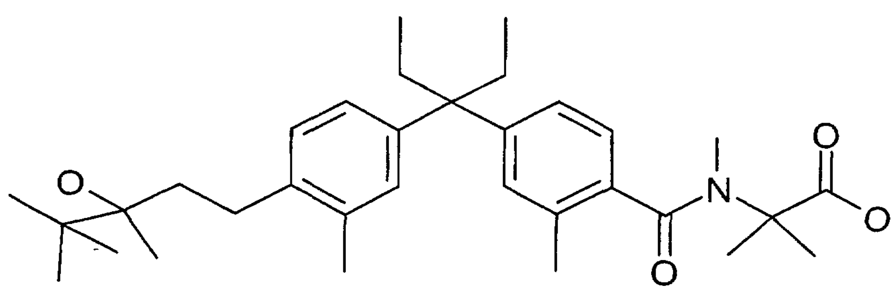

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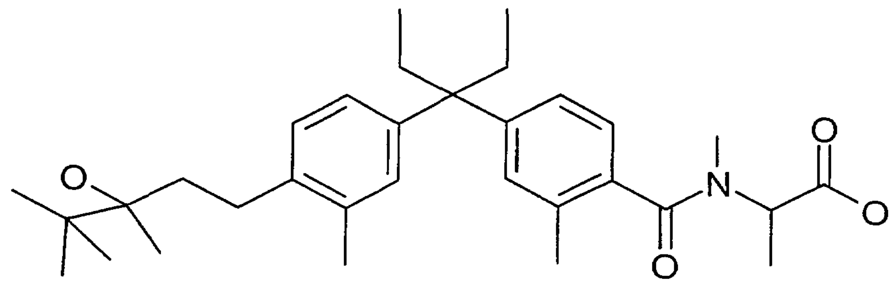

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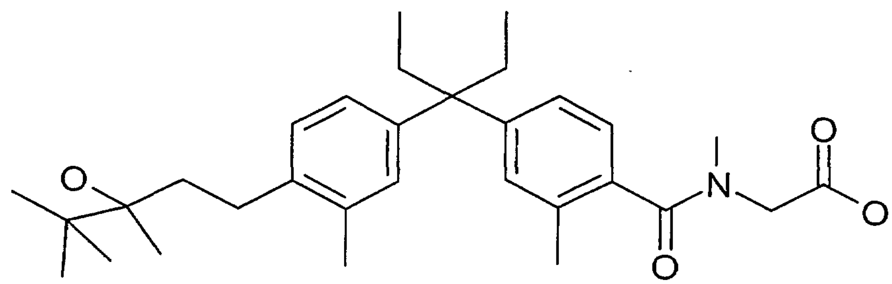

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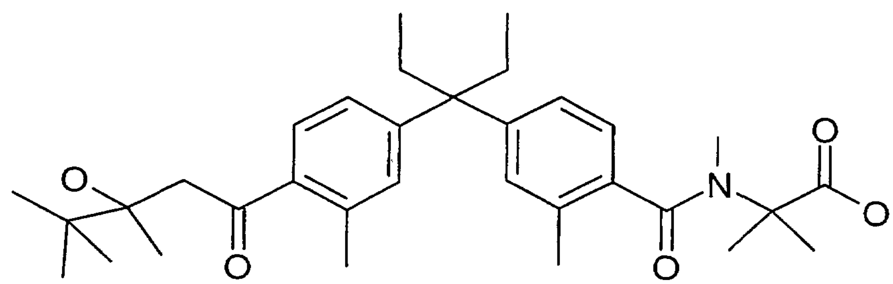

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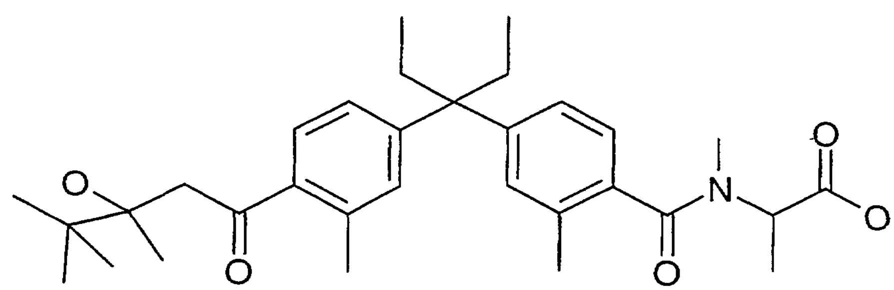

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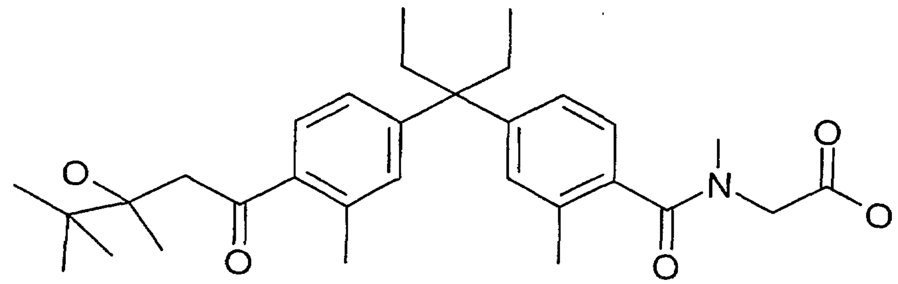

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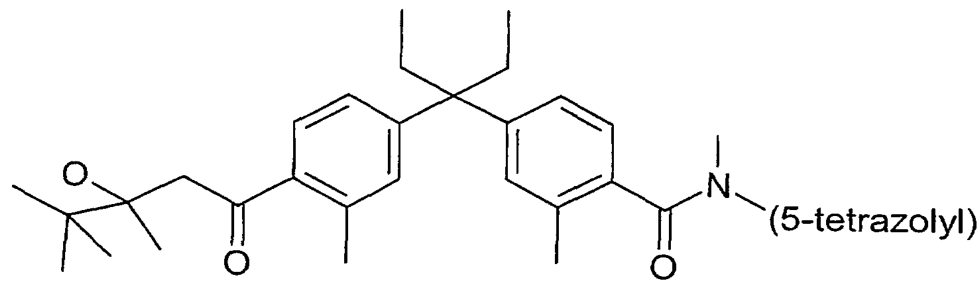

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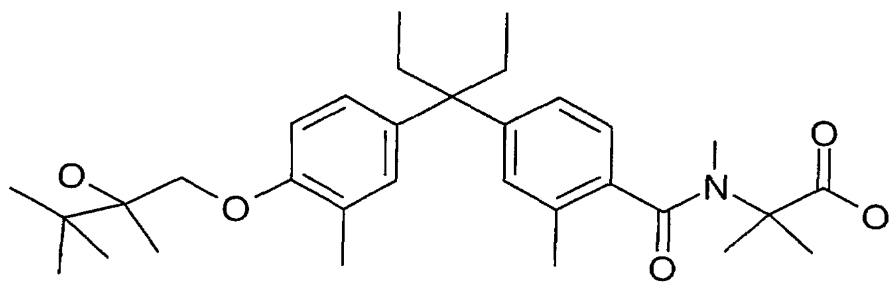

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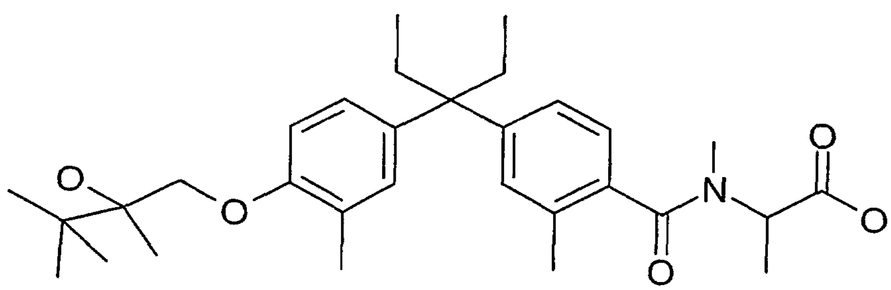

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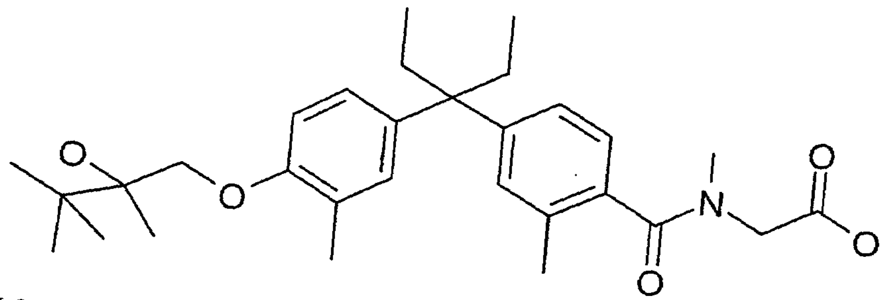

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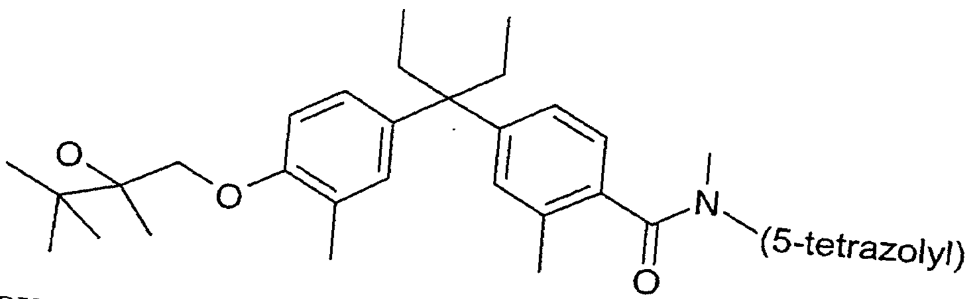

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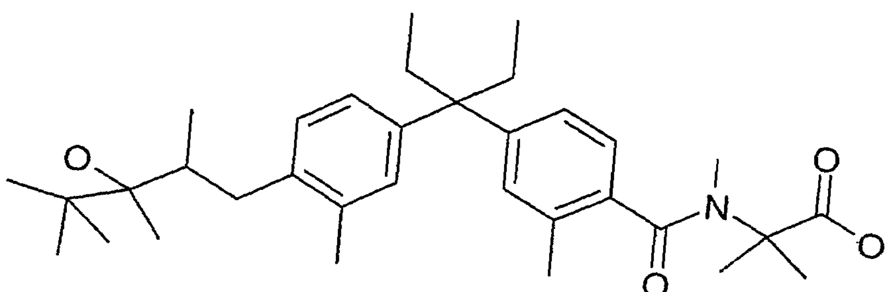

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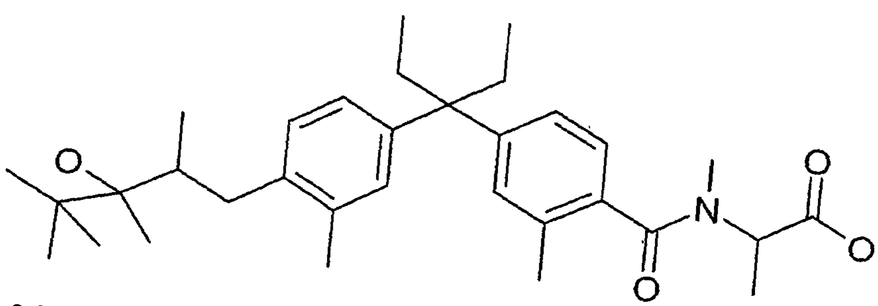

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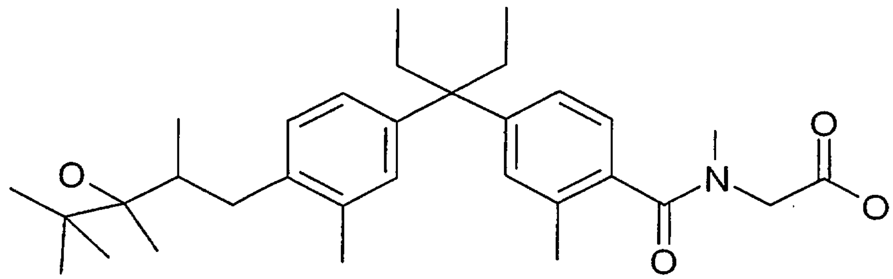

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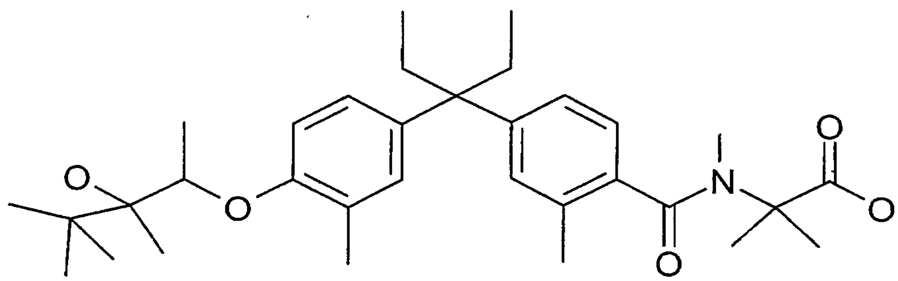

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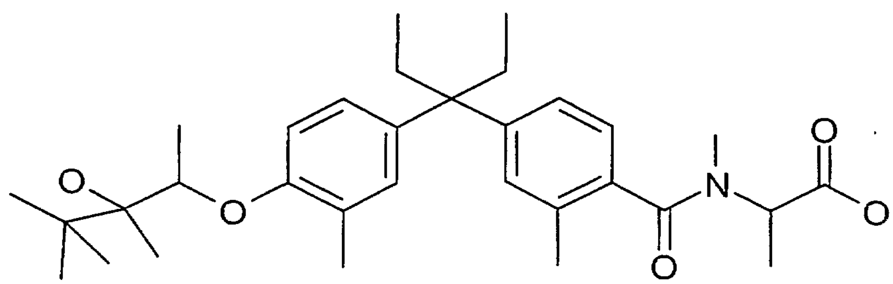

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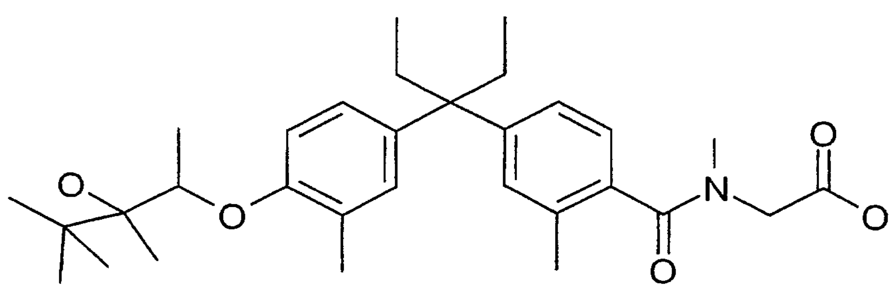

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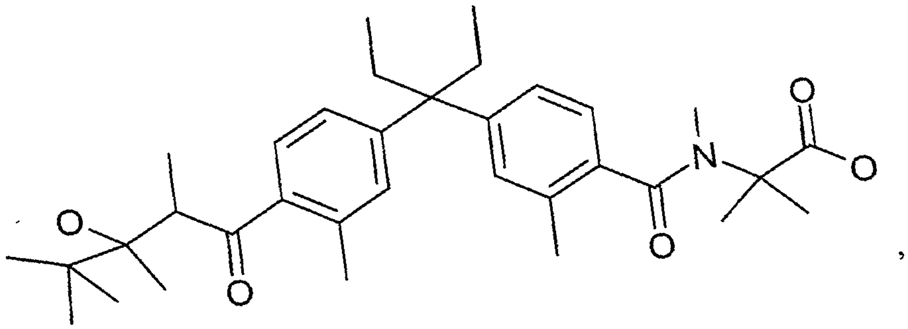

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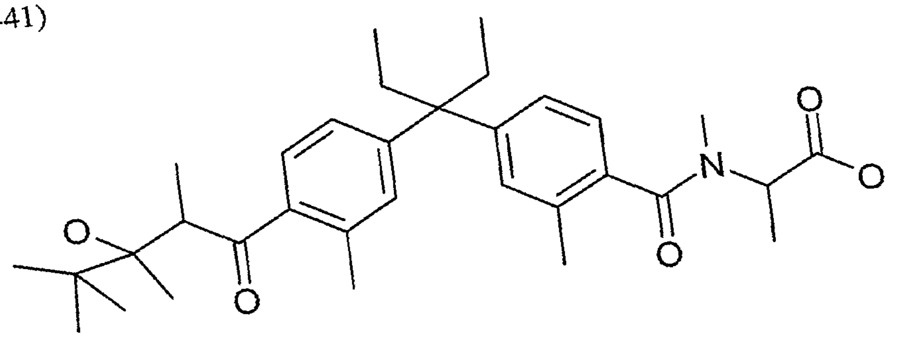

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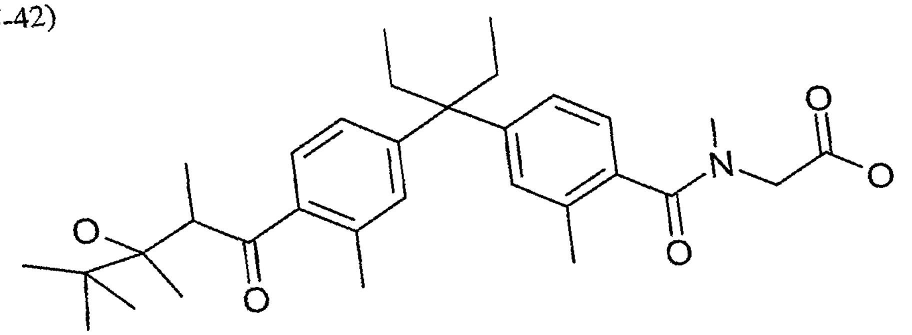

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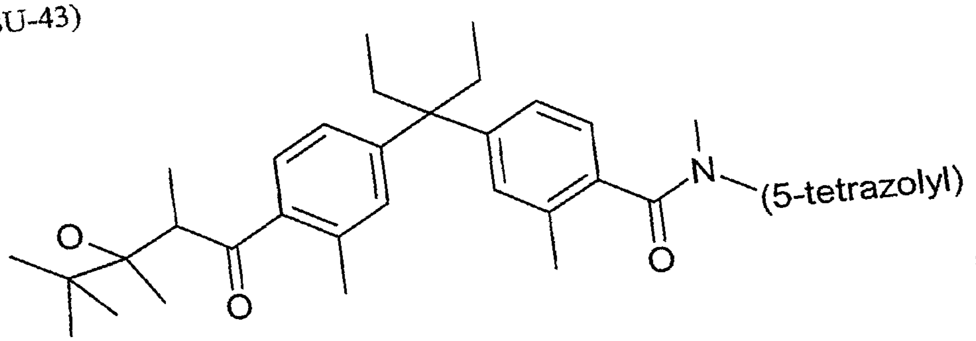

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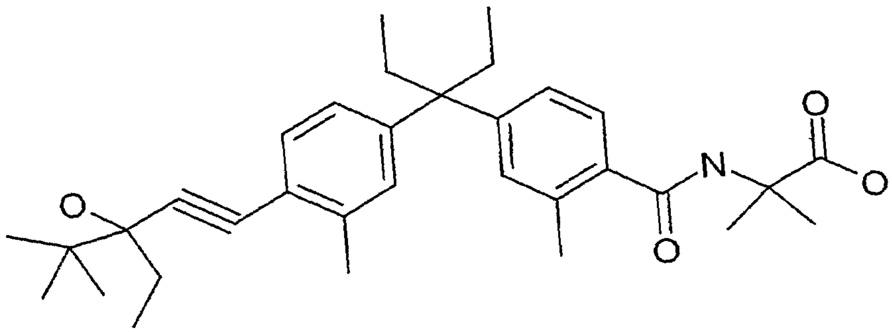

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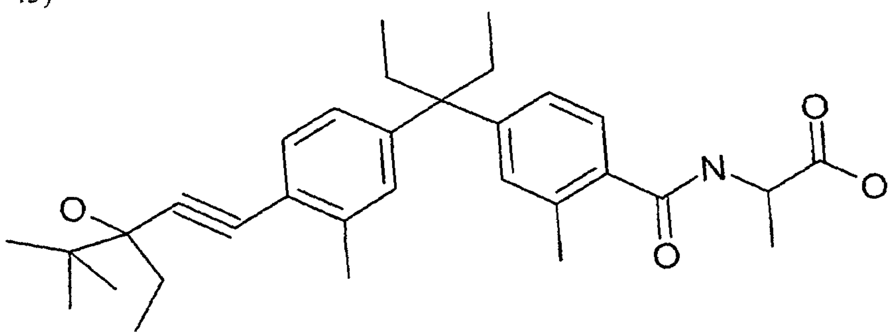

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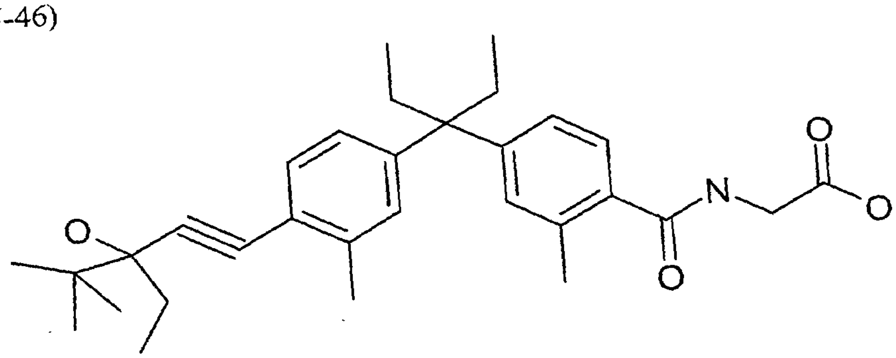

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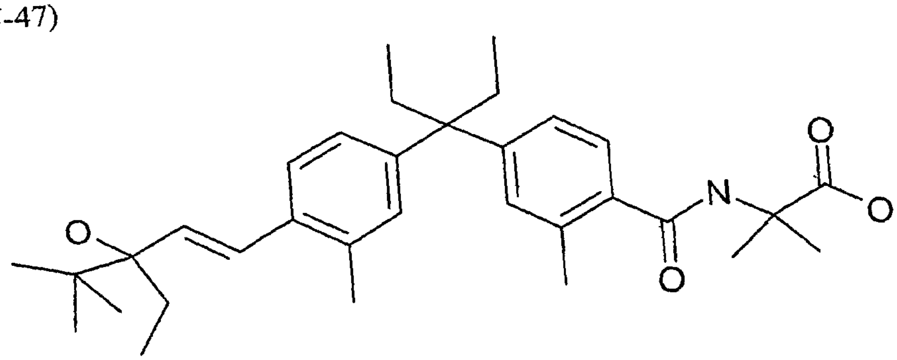

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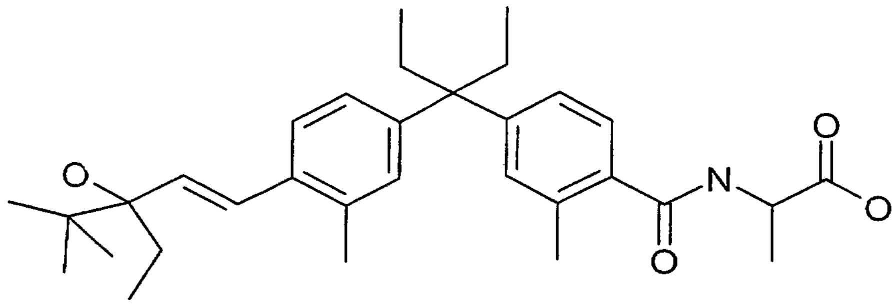

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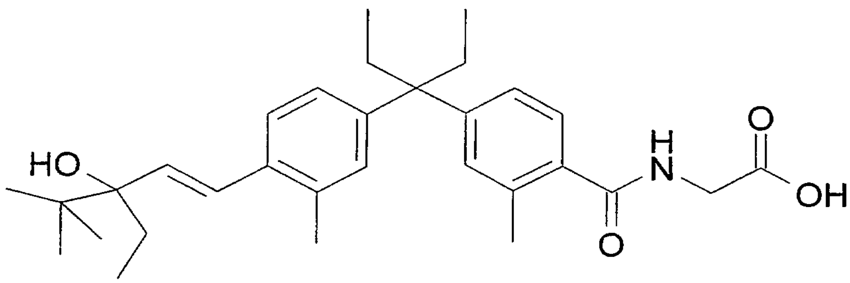

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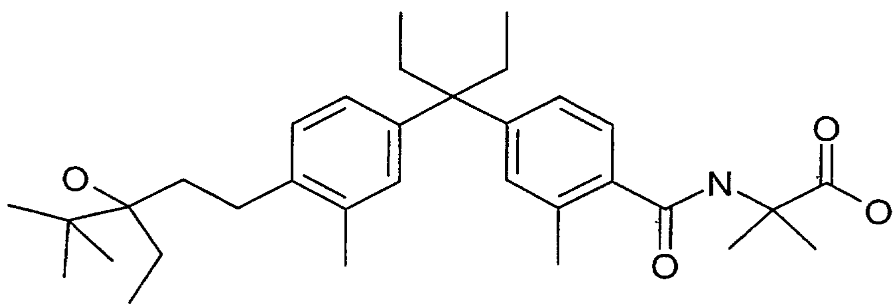

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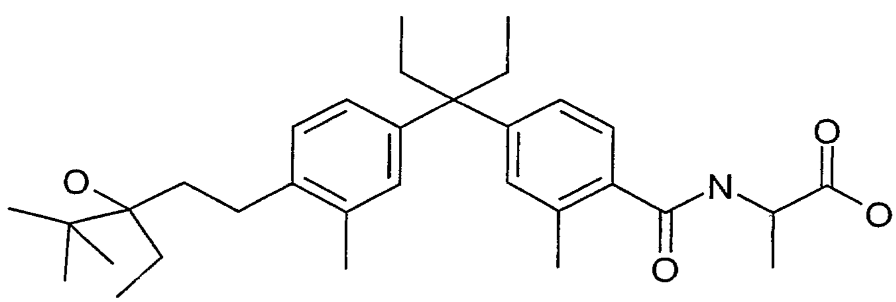

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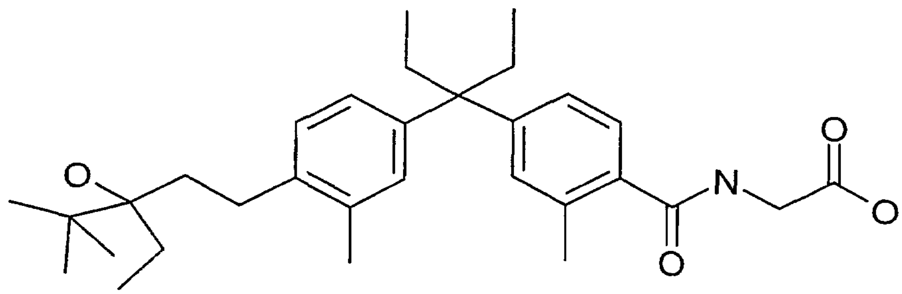

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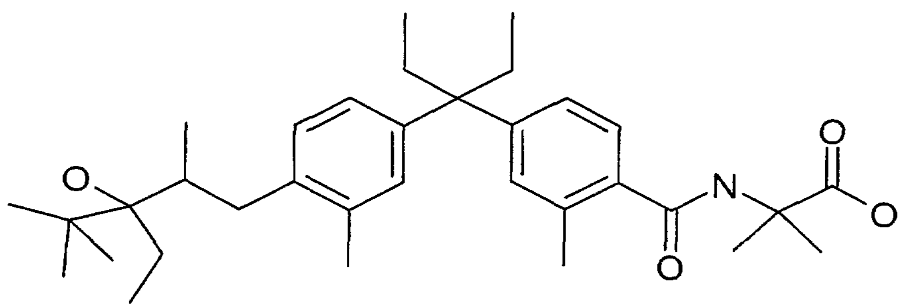

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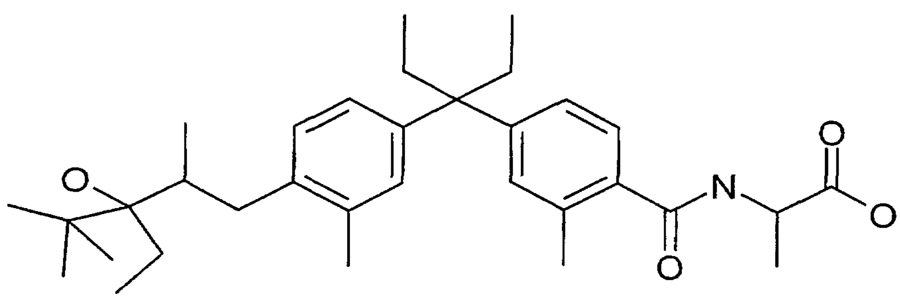

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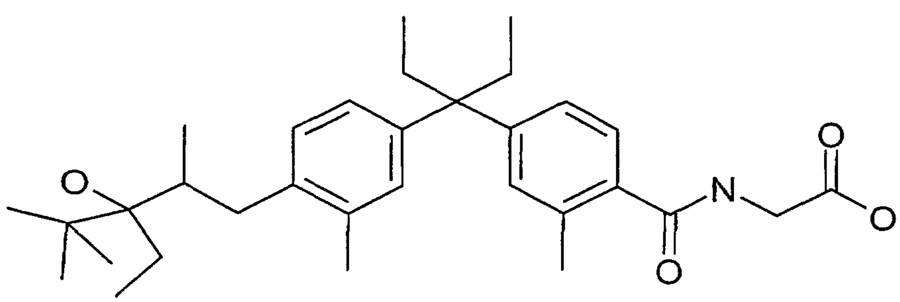

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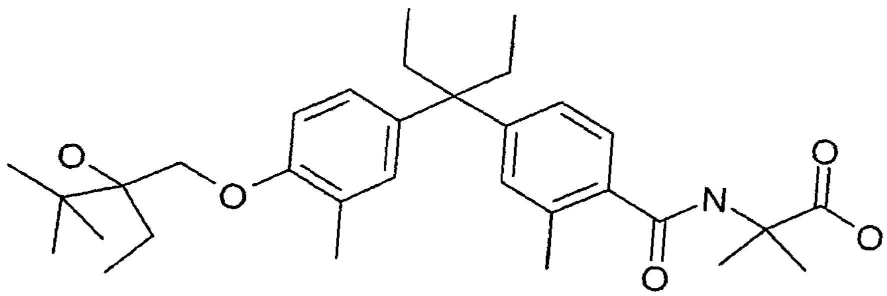

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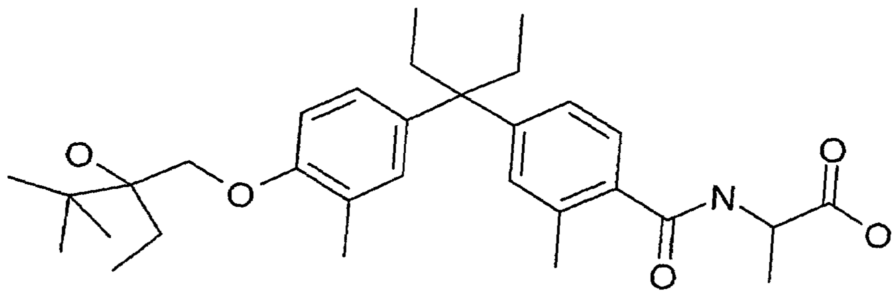

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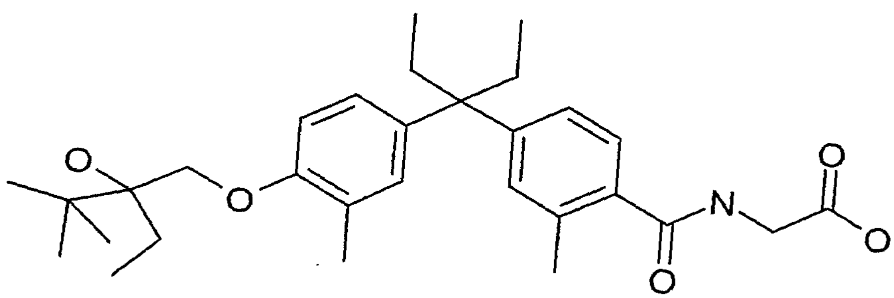

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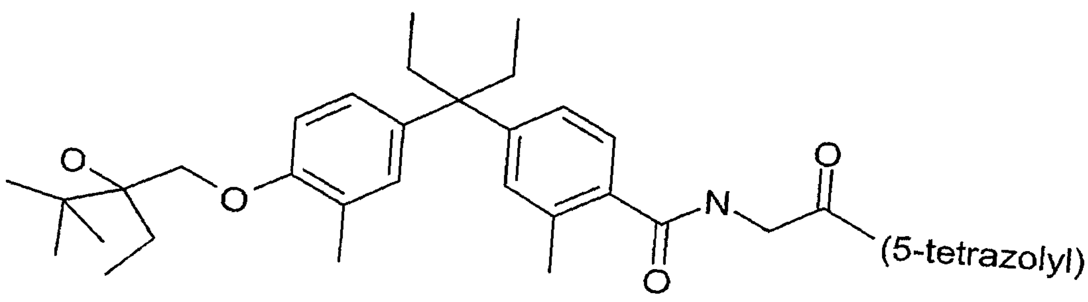

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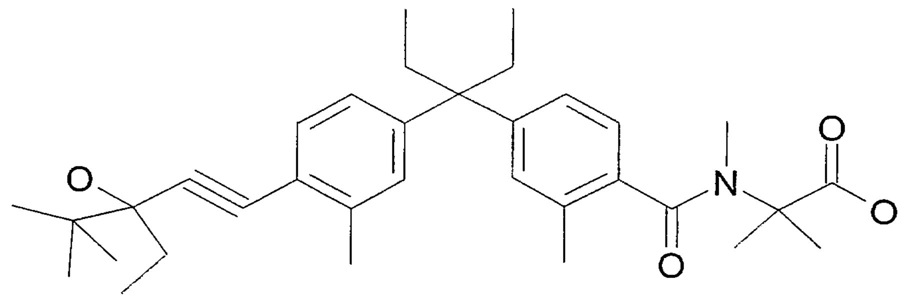

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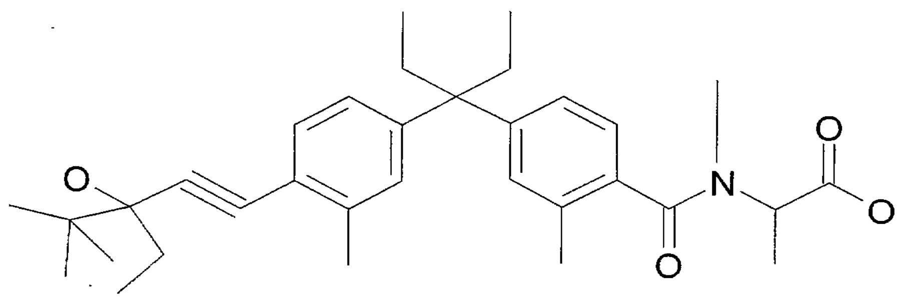

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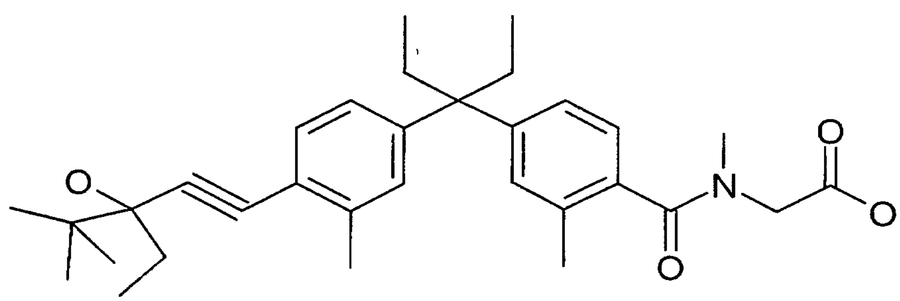

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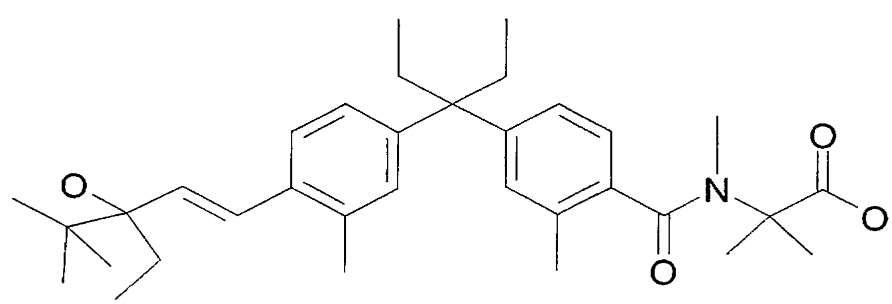

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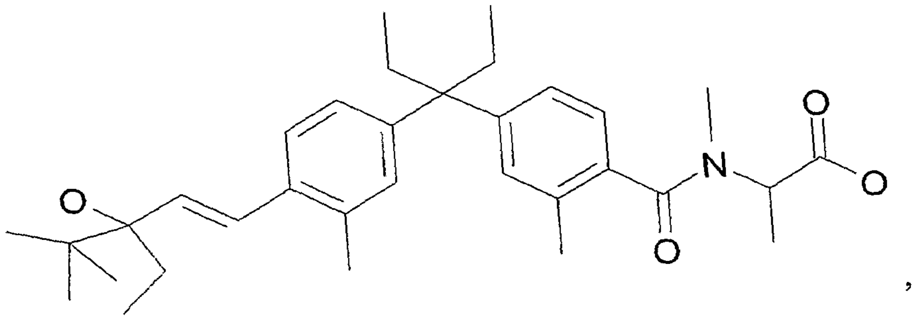

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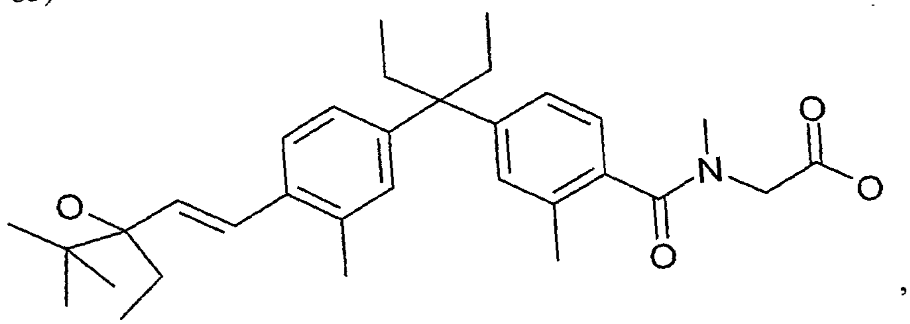

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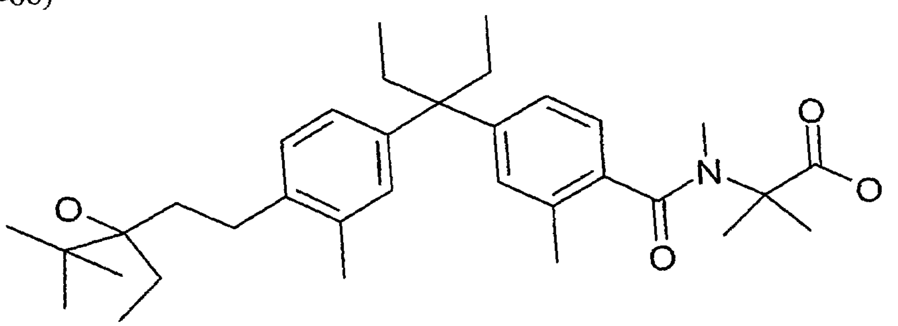

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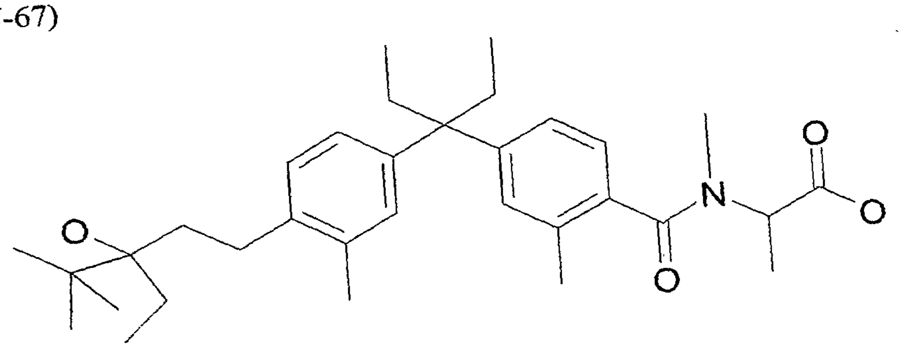

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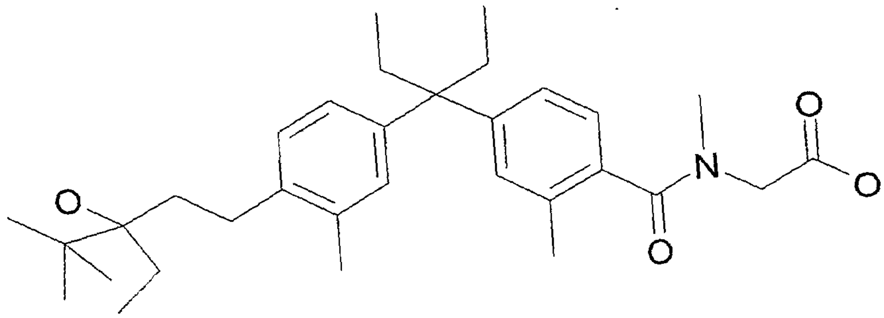

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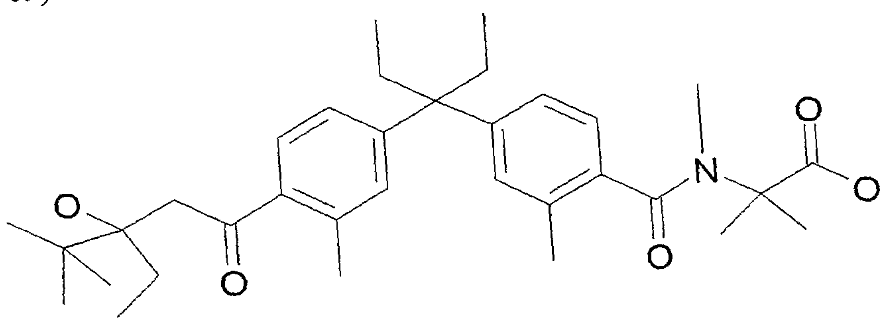

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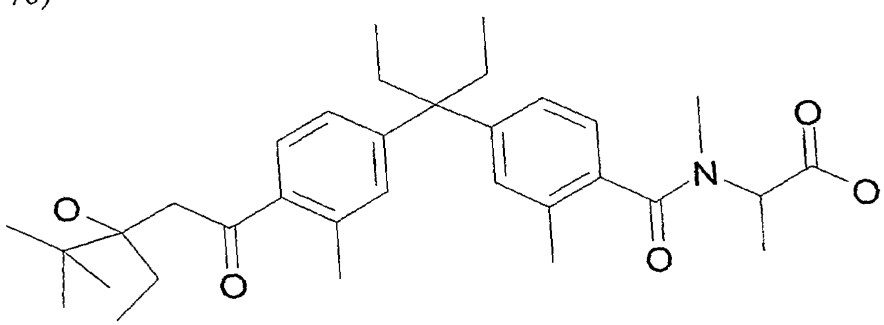

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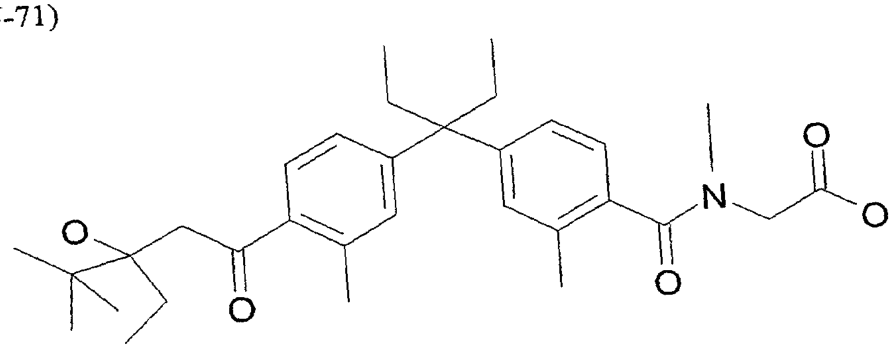

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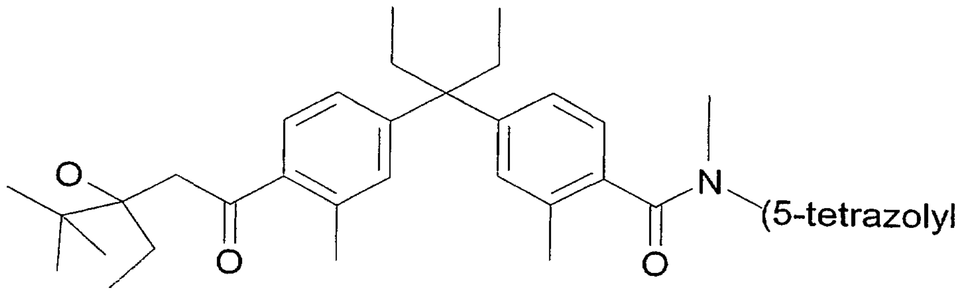

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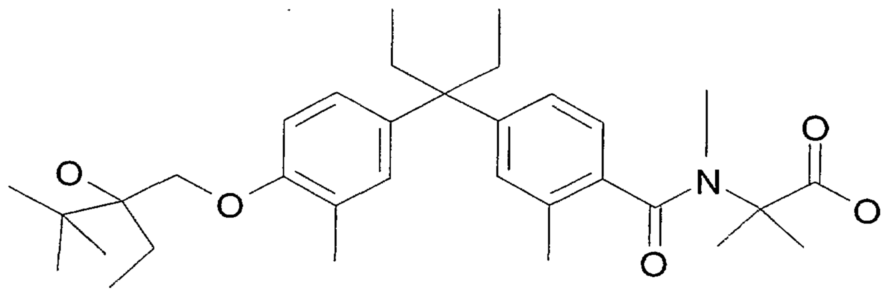

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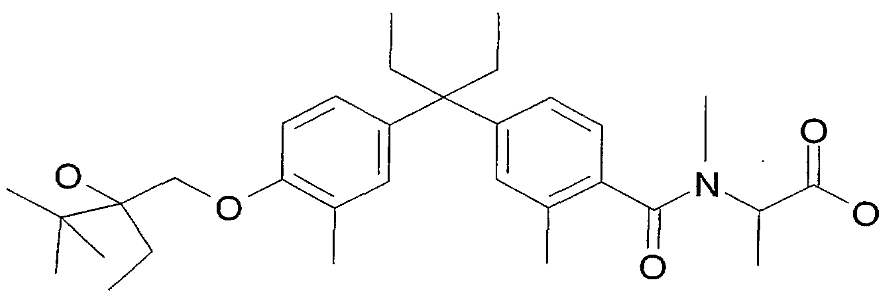

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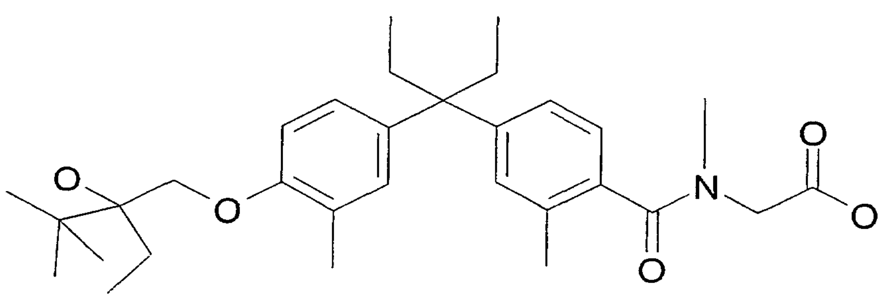

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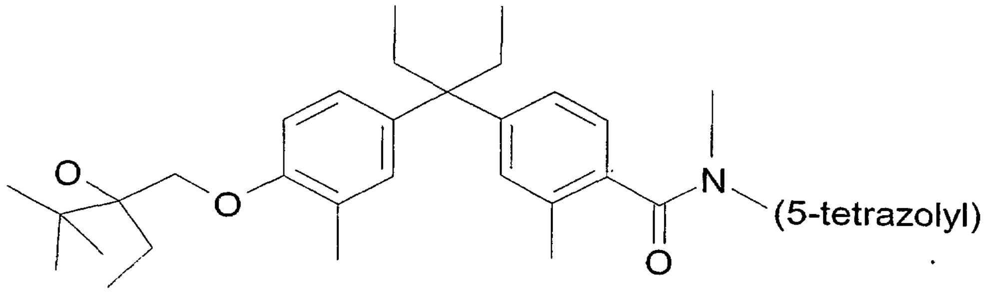

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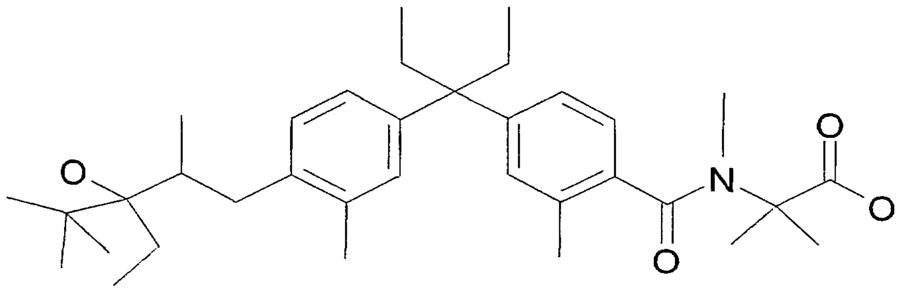

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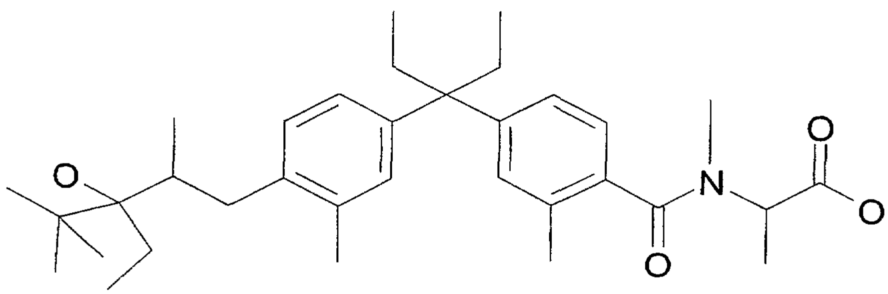

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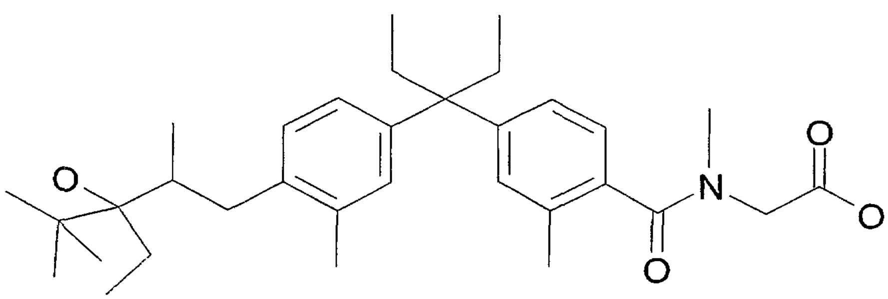

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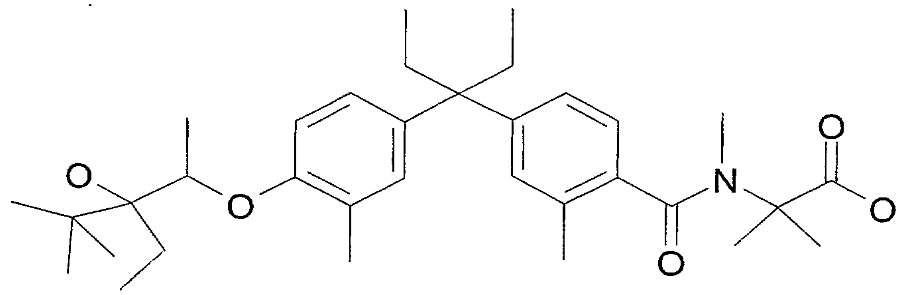

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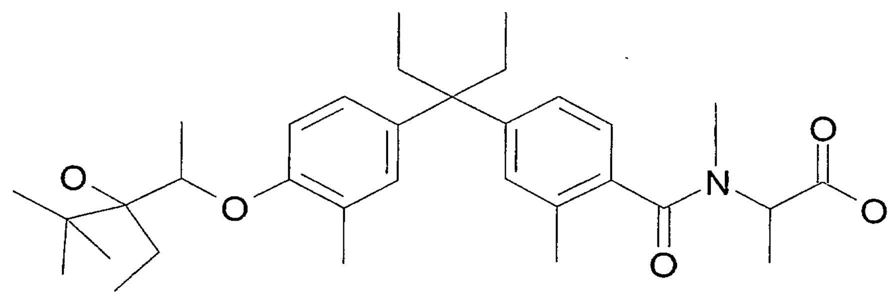

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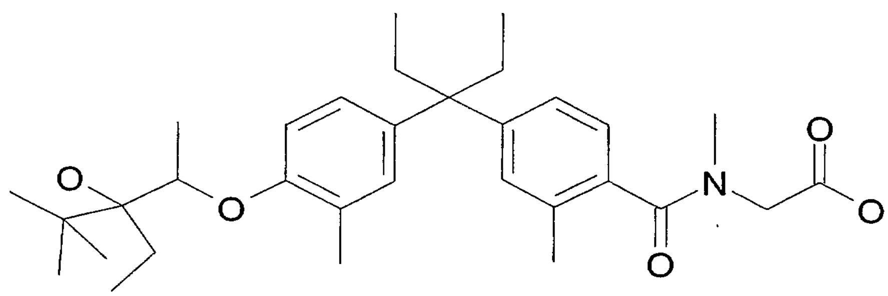

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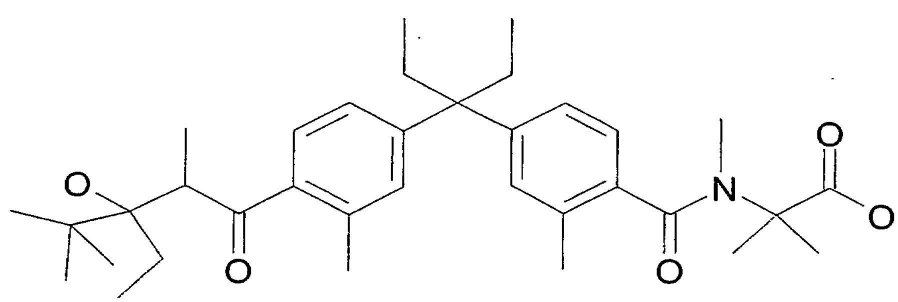

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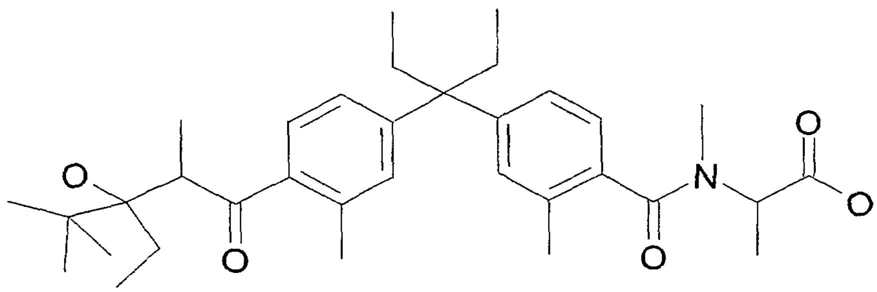

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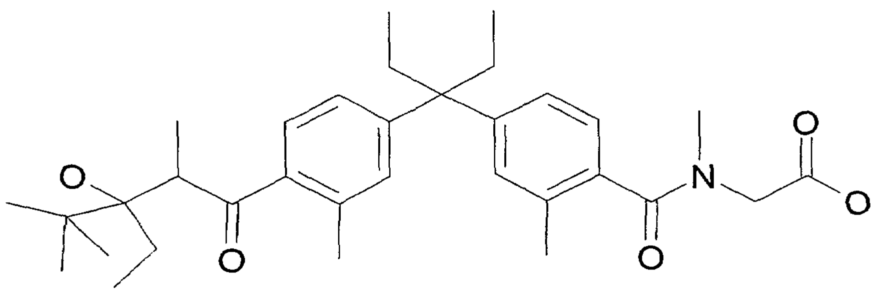

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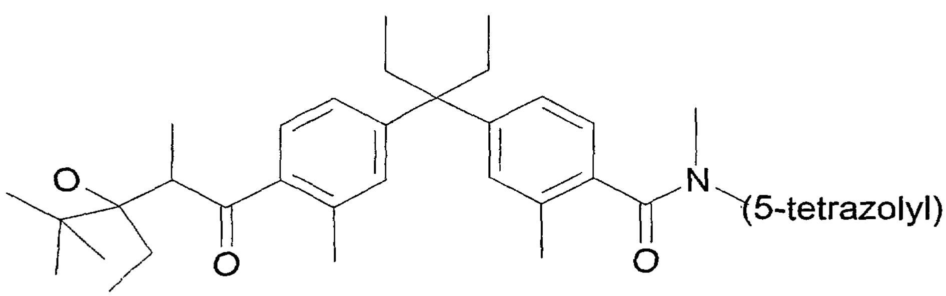
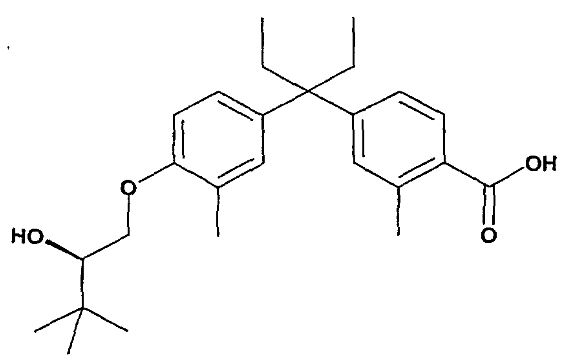
TBU-86)

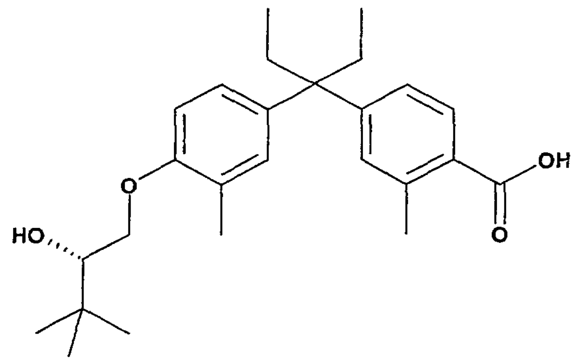


.

10. The compound or a pharmaceutically acceptable salt or ester prodrug derivative of the compound represented by the formula:



or



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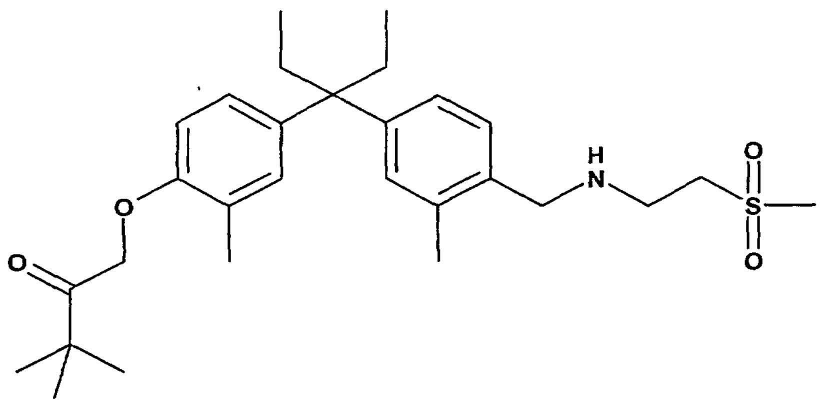
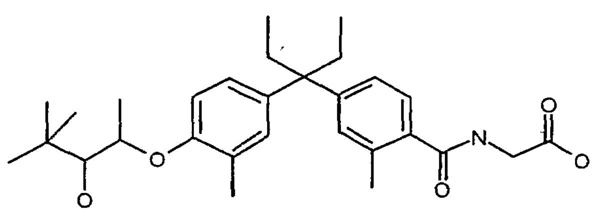


.

11. The compound or a pharmaceutically acceptable salt or ester prodrug derivative of the compound represented by the formula:



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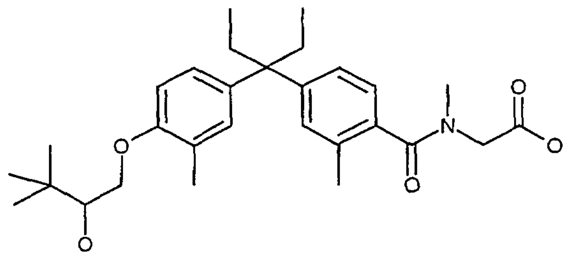

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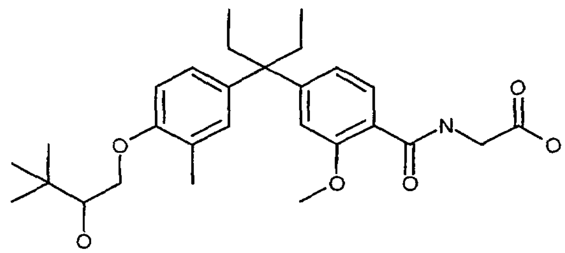

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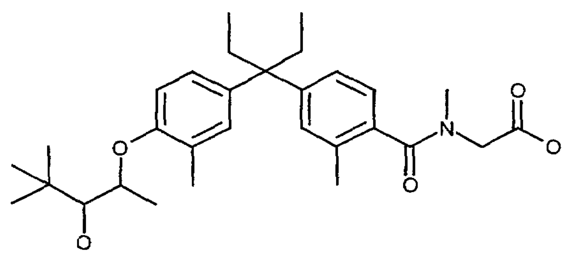
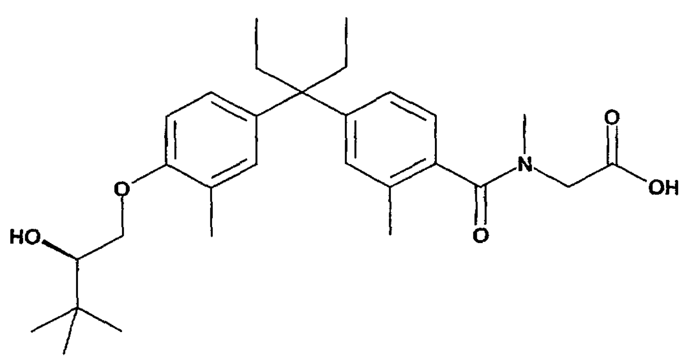
or

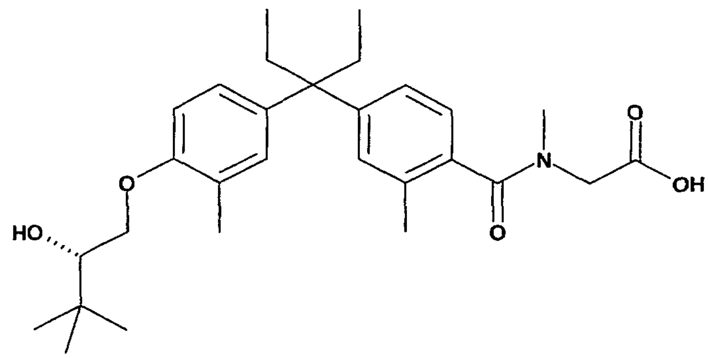


.

12. The compound or a pharmaceutically acceptable salt or ester prodrug derivative of the compound represented by the formula:



or



13. The prodrug derivative of a compound of claim 1 to 12 wherein the prodrug is a methyl ester, ethyl ester N,N-diethylglycolamido ester or morpholinylethyl ester.

14. The salt derivative of a compound of claim 1 to 12 wherein the salt is sodium or potassium.

15. A pharmaceutical formulation comprising a compound of claim 1 to 12 together with a pharmaceutically acceptable carrier or diluent.

16. A formulation for treating osteoporosis comprising:

Ingredient (A1): a vitamin D receptor modulator of claim 1 to 12;

Ingredient (B1):

one or more co-agents selected from the group consisting of:

a. estrogens,
b. androgens,
c. calcium supplements,
d. vitamin D metabolites,
e. thiazide diuretics,
f. calcitonin,
g. bisphosphonates,
h. SERMS, and
i. fluorides; and

Ingredient (C1): optionally, a carrier or diluent.

17. The formulation of claim 16 wherein the weight ratio of (A1) to (B1) is from 10:1 to 1:1000.

18. A formulation for treating psoriasis comprising:

Ingredient (A2): a vitamin D receptor modulator of claim 1 to 11;

Ingredient (B2):

one or more co-agents that are conventional for treatment osteoporosis selected from the group consisting of:

a. topical glucocorticoids ,

b. salicylic acid,

c. crude coal tar; and

Ingredient (C2): optionally, a carrier or diluent.

19. The formulation of claim 18 wherein the weight ratio of (A2) to (B2) is from 1:10 to 1:100000.

20. A method of treating a mammal to prevent or alleviate the pathological effects of acne, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone fracture healing, breast cancer, prostate cancer, colon cancer, diabetes, Type I, host-graft rejection, humoral hypercalcemia , induced diabetes, leukemia, lupus, multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, phoriatic arthritis, psoriasis, renal failure, renal osteodystrophy, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, skin cell protection from Mustard vesicants, and wrinkles; wherein the method comprises administering a pharmaceutically effective amount of at least one compound of claim 1 to 12.

21. The method of claim 20 for the treatment of psoriasis.

22. The method of claim 20 for the treatment of osteoporosis.

23. A method of treating or preventing disease states mediated by the Vitamin D receptor, wherein a mammal in need thereof is administered a pharmaceutically effective amount of a compound of claim 1 to 12.

24. A compound as claimed in claim 1 to 12 for use in treating a mammal to prevent or alleviate the pathological effects of acne, alopecia, Alzheimer's disease, autoimmune induced diabetes, bone maintenance in zero gravity, bone fracture healing, breast cancer, prostate cancer, colon cancer, diabetes, Type I, host-graft rejection, humoral hypercalcemia , induced diabetes, leukemia, lupus, multiple sclerosis, insufficient sebum secretion, osteomalacia, osteoporosis, insufficient dermal firmness, insufficient dermal hydration, phoriatic arthritis, psoriasis, renal failure, renal osteodystrophy, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, and wrinkles.

25. A method of treating a mannal to prevent or alleviate the effect of Mustard by administering a pharmaceutically effective amount of a formulation comprising the compound of claim 1 to 12 alone or together with a pharmaceutically acceptable carrier or diluent thereof.

26. A compound as claimed in any one of claim 1 to 12 for use in treating or preventing disease states mediated by the Vitamin D receptor.

27. A compound as claimed in Claim 1 substantially as hereinbefore described with reference to any of the Examples.

28 . A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described with reference to any of the Examples.

29. The use of a compound as claimed in claim 1 substantially as herein described with reference to any of the Assays and Tables for mediating the Vitamin D receptor.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 03/35055

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C59/90 C07C62/24 C07C69/78 C07C235/34 C07C311/50
C07C317/28 C07D257/06 C07D277/34 A61K31/12 A61K31/165
A61K31/18 A61K31/19 A61K31/192 A61K31/235 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 218 430 B1 (ELIZABETH A. ALLEGRETTO ET AL) 17 April 2001 (2001-04-17) cited in the application the whole document	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° *Special categories of cited documents :*

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" *document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)*
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to *involve an inventive step when the document is taken alone*
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2004	14/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cooper, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/35055

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/426

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 April 2004	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cooper, S

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-23,25,29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 03/35055

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6218430 B1	17-04-2001	AT 253032 T	15-11-2003
		AU 756336 B2	09-01-2003
		AU 5485299 A	14-03-2000
		CA 2339775 A1	02-03-2000
		DE 69912450 D1	04-12-2003
		DK 1107940 T3	08-03-2004
		EP 1107940 A1	20-06-2001
		JP 2002523388 T	30-07-2002
		WO 0010958 A1	02-03-2000